

***Screening for Mycobacterium tuberculosis in The U.S. Military:
Considerations for a Cost-Effectiveness Model***

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Executive Summary:

Background: In the late 1980s and early 1990s, an emergence of multi-drug-resistant tuberculosis sparked widespread epidemics across the United States. In efforts towards tuberculosis elimination, the CDC and the American Thoracic Society recommended continued and heightened screening activities, including development of improved diagnostic and treatment methods, improved vaccines and establishment of broad-based partnerships between the private health sector and public health programs. Traditionally, military rates have been below those experienced in the general population. However, the potential for large scale exposure due to environmental factors in the presence of a single index case is of concern. The current purified protein derivative tuberculosis skin test (PPD/TST) offers a long history of documented use, perceived simplicity of administration and low test cost. However, great concern for the programmatic short-comings of current military screening programs, which use PPD/TST, exists. QuantiFERON-TB (CSL Biosciences, Victoria, Australia), a laboratory based antigen test, has recently become available for *M. tuberculosis* screening. QuantiFERON-TB offers potentially equivalent immunological sensitivity and specificity to that of the PPD/TST, obviates the need for a second screening visit to read the test, and potentially facilitates recording of large numbers of results through direct entry by the laboratory.

Objective: The initial goal of this project was to perform a cost-effectiveness evaluation of QuantiFERON-TB compared to PPD/TST in the U.S. military. However, a paucity of quantitative programmatic evaluation data exists (e.g., percentage of individuals who receive timely screening, and the accuracy with which PPD/TST is placed and interpreted). The lack of data prohibits a rigorous quantitative cost-effectiveness analysis of tuberculosis screening. Consequently, in this report a qualitative approach is taken. This report describes the current tuberculosis screening programs in the Navy (including Marines), Army and Air Force. The programmatic aspects of tuberculosis screening which would impact a comparison of the current PPD/TST strategy and a QuantiFERON-TB strategy are discussed. For illustrative purposes the costs of the screening related events associated with each strategy are estimated in Army recruits. Recommendations are made for improvement of the current tuberculosis screening strategies, considering all aspects of tuberculosis screening unique to the military.

Methods: Through a modified three stage Delphi technique, descriptive and educational qualitative data were collected from individuals in the military with experience in tuberculosis control. Preventive medicine officers at the Walter Reed Army Institute of Research (WRAIR) identified individuals appropriate for participation. During Stage 1, service-specific focus groups were conducted to collect information on screening protocols and address service-specific concerns. During Stage 2 individuals targeted in Stage 1 were contacted for further discussions on ongoing evaluations and to collect quantitative data (when

possible). During Stage 3, a questionnaire was distributed via e-mail. The data collected in Stage 3 was used to verify and expand upon information collected in Stage 1. The costs associated with an individual screening event were estimated for each strategy including, test costs, materials cost, personnel costs, and lost productivity for screening visits. The Army training setting was used for baseline cost estimates.

Results: Nineteen individuals were identified for participation (the WRAIR group originally identified 15 and four were added as recommendations). These individuals were invited to participate in the study. 68% (13/19) participated in Stage 1. Four individuals participated in Stage 2. Each of the three services was represented in Stage 2. Stage 1 revealed a high degree of variability in screening practices across the services in terms of screening frequency, success with follow-up visits, and willingness to change from a PPD/TST strategy to a QuantiFERON-TB strategy. While all services cited concern with the variability in interpretation of the PPD/TST, each service had unique difficulties with the logistics of follow-up. Variability in the quality of reporting systems was also observed. Several respondents wanted further documentation and confirmation of QuantiFERON-TB operating characteristics based on empiric evidence. Disparity in opinions on the quality of the PPD/TST sensitivity and specificity was also observed. All participants desired improved standardization and education. The PPD/TST cost \$18.33 per individual screening event, while QuantiFERON-TB cost \$17.08 per individual screening event in the Army training setting. These cost estimates were sensitive to setting changes, cost of screening visit, as well as wage and rank of individual being screened. However, across most assumptions QuantiFERON-TB cost less than or equal to the PPD/TST strategy per screening event.

Discussion: In some settings QuantiFERON-TB offers a higher practical benefit than in others. Difficulty in accessing laboratory equipment and data poses difficulty in field settings. While, QuantiFERON-TB costs less per screening event than PPD/TST, primarily due to decreased lost productivity costs, the cost estimates should be viewed with caution. The estimates do not include numerous aspects of the screening process (medical costs of unnecessary work-ups associated with false positive results, costs associated with a second PPD/TST to replace a test placed but never read, etc.) and cost-of-illness related costs (i.e., costs of a missed case of TB). These costs will be substantially affected by the ability of each test to accurately identify positive individuals. Furthermore, the cost estimates may not be generalizable to all services. Instead, they are meant to offer a baseline for discussions on the potential factors that warrant consideration in future evaluations. Establishment of improved training and quality assurance capacities for PPD/TST strategies is necessary. Improved distribution of information on the immunological sensitivity and specificity of QuantiFERON-TB is necessary, due to lack of general knowledge on the performance of QuantiFERON-TB. QuantiFERON-TB has the potential to offer substantial practical benefits to the military.

Background:

In the late 1980s and early 1990s, an emergence of multi-drug-resistant tuberculosis sparked widespread epidemics across the United States (Burwen, 1995; Cartwell, 1994). In 1995, tuberculosis ranked seventh among the top ten most frequently reported infectious diseases as reported by the Centers for Disease Control and Prevention (CDC). However, due to stronger control efforts in identification of infection and treatment of tuberculosis, a declining number of cases were reported each year (CDC, 1999a). In 1998, a total of 18,361 tuberculosis cases were reported to the CDC representing a 7.5% decrease from 1997 and 31% from 1992 (MMWR, 1999a; CDC, 1999a). The annual cost of tuberculosis in the United States approaches \$1 billion (Brown, 1995). In efforts towards tuberculosis elimination, the CDC and the American Thoracic Society (ATS) of the American Lung Association recommend continued and even heightened screening activities, including development of improved diagnostic and treatment methods, improved vaccines and establishment of broad-based partnerships between the private health sector and public health programs (MMWR, 1999a; TB Notes, 1999; CDC, 1999b; MMWR, 1999b).

Tuberculosis is a chronic bacterial infection which usually manifests in the lower respiratory tract (OnHealth, 2000). At least 90% of individuals infected with *Mycobacterium tuberculosis* will not develop acute clinical signs of active disease. Yet, 10% will develop symptoms: cough with bloody sputum, fatigue, weight loss, fever (night sweats) and pain in the chest, kidneys and back. The risk of disease after infection is highest among late adolescents and young adults (Comstock, 1974). While infection with *M. tuberculosis* does not imply infectiousness, the bacteria can become active after long periods of dormancy leading to symptomatic disease, during which *M. tuberculosis*, as an air borne pathogen, can be highly infectious (ATS, 1990). Consequently, treatment efforts must target all infected individuals, those with active disease, as well as those with latent disease.

Tuberculosis in the Military:

In the military, lower crude rates of tuberculosis have been observed than those for the nation as a whole (Shanawani, 1998). In the Air Force, an average of 25 positive IPPD tests per 1000 tested were observed using Air Force Reportable Events Surveillance System (AFRESS) data for CY 1998 (unpublished data, CPT. K. Neuhauser, July 26, 1999). The rate of active TB cases that have occurred in AFRESS for all beneficiaries was 1.8 per 100,000 for CY 1997 and 1.9 per 100,000 for CY 1998. The Army reported 971 incident tuberculosis cases during a 17 year period (1980 to 1997) (Camarca, 1999). Annual rates of 3.27 to 4.11 cases per 100,000 have been estimated (Shanawani, 1998). Army hospitalizations for tuberculosis during this period declined from 16 per 100,000 to 5 per 100,000. The decline was more significant in males than in females and hospitalization rates were highest in hospitals located in South Korea. This study credited efforts of the Army Tuberculosis Control Program for low tuberculosis incidence and the decline in hospitalizations (Camarca, 1999). In an analysis of current and new hospital employees (Walter Reed Army Medical Center, WRAMC) the 2-year conversion rate for the hospital as a whole was 2.3% (55/2367) (MSMR, 1995). Estimated 2-year conversion rates among active duty and civilian personnel at WRAMC was 3.1% (39/1254) and 1.4% (16/1113), respectively (MSMR, 1995). In 1995, at all Army sites, only 2 cases of tuberculosis were reported in the active duty Army (MSMR, 1995).

Diagnosis of *M. tuberculosis*:

The tuberculin skin test (TST), which detects cell mediated immune responses, remains the most widely used method of detection for *M. tuberculosis* infection (ATS, 1990; Streeton 1998). The most commonly used preparation is purified protein derivative (PPD) which is applied through intracutaneous injection by either the Mantoux or the multiple injection techniques. Features of a reaction to PPD include, a delayed course (peak at 24 hours or more), indurated character of reaction, and occasional vesiculation and necrosis (ATS, 1990). Hypersensitivity is maximal at 48 to 72 hours (ATS, 1990). A reaction can be

indicative of a natural infection with *M. tuberculosis*, infection with a variety of non-tuberculosis mycobacteria or BCG vaccination (ATS, 1990). The American Thoracic Society (ATS) describes the process of reading the Mantoux technique as such:

“Tests should be read 48 to 72 hours after injection. Reading should be performed in good light with the forearm slightly flexed at the elbow. The basis of reading is the presence or absence of induration, which may be determined by inspection (from a side view against the light as well as by direct light) and by palpation. The diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters.” (ATS, 1990)

The size of the induration is used to define infection. The guidelines for induration size categorization vary by the patient’s epidemiological and environmental risk of infection (Sbarbaro, 1985). An induration threshold of 5mm is classified as positive in: 1) persons with HIV infection; 2) persons with a close recent contact with infectious tuberculosis; and 3) persons with tuberculosis positive chest radiographs (ATS, 1990; MMWR, 1995). A reaction 10 mm is considered positive in: 1) foreign born individuals; 2) intravenous drug users; 3) medically under-served low income populations; 4) residents of long-term care facilities; and 5) persons with medical conditions reported to increase risk (ATS, 1990; MMWR, 1995). A reaction of 15mm is classified as positive in all other individuals (ATS, 1990; MMWR, 1995). Evaluation of application of these guidelines in the military are currently under study (unpublished data, K. Neuhauser, AFEB, February, 1999)

QuantiFERON-TB offers an alternative to traditional PPD/TST screening. QuantiFERON-TB requires a 10ml blood draw. The heparinised blood is stimulated in vitro with a negative (Nil antigen) and a positive control antigen (Mitogen), a *M. tuberculosis* specific identifying antigen (Human PPD), and a *M. avian* antigen (Avian PPD) (Rothel, 2000). The Avian PPD is used to discriminate between *M. tuberculosis* and atypical mycobacterial infection. The absence of a gold standard beyond PPD reactivity, to which new tests can be compared, complicates comprehensive evaluation of QuantiFERON-TB. Newly available tests can presently only achieve equivalence to the PPD/TST. Preliminary analyses of 952 volunteers (701 civilian participants and 251 military

recruits) in Australia indicated strong agreement and no significant difference between the PPD/TST and QuantiFERON-TB tests (Streeton, 1998). A specificity of 97.6% was estimated in individuals with no known exposure to tuberculosis. Sensitivities ranged from 83% in individuals with proven active disease, to 89.6% in untreated PPD/TST reactors. Additionally, QuantiFERON-TB identified 43% of individuals exposed to tuberculosis with negative PPD/TST results (Streeton, 1998).

A recent CDC multi-site trial compared QuantiFERON-TB to PPD/TST in 1326 subjects stratified by risk category (unpublished data, GH Mazurek, CDC). In this study 84.9% agreement and high intermediate correlation ($\kappa=0.56$) was observed for the combined group of low and high risk subjects.

Converse et al., compared QuantiFERON-TB to PPD/TST in 66 intravenous drug users (Converse, 1997). This study found 100% agreement in HIV negative, PPD/TST positive participants. However, a 54% specificity was observed using PPD/TST as the gold standard. Overall an adjusted agreement of 46% was observed in HIV negative participants, implying intermediate correlation (Converse, 1997). Similarly, Kimura et al., evaluated QuantiFERON-TB compared to PPD/TST in 467 intravenous drug users (Kimura, 1999). While, in this study very few PPD/TST reactors were missed by QuantiFERON-TB, overall in HIV negative participants a 59% agreement and weak correlation between QuantiFERON-TB and PPD/TST was observed. This result was due to PPD/TST non-reactors with positive QuantiFERON-TB results.

Keep et al., evaluated PPD and QuantiFERON-TB in 1,701 Navy recruits at Great Lakes, Naval Recruiting Station (personnel communication, MAJ Keep, 1999). The study identified a kappa of 0.34 where 28 PPD reactors were QuantiFERON-TB negative, 117 QuantiFERON-TB positive individuals with negative PPD results and 1,556 agreements.

QuantiFERON-TB appears to offer a sensitivity equivalent to that of PPD/TST. However, specificity of QuantiFERON-TB is difficult to assess until analysis of available clinical trial data is completed. Currently, the immunological sensitivity of PPD/TST is believed to range from 70 to 90% (Heubner, 1993).

Consequently, in the absence of immunological or histopathological confirmation, it is difficult to determine true infection status in patients with discordant results (Converse, 1999; Streeton, 1998).

The specificity of the PPD/TST is influenced by exposure to non-tuberculosis mycobacteria, the tuberculin PPD used and BCG vaccination, as well as the subjective nature of both placing and reading the PPD/TST (Chaisson, AIDS, 1996). Consequently, the sensitivity and specificity of QuantiFERON-TB can be considered across two domains: immunological characteristics of the test (as described above, including the ability to discriminate between *M. tb* and non-tuberculosis mycobacteria) and the programmatic sensitivity and specificity of the screening strategy. Programmatic sensitivity and specificity include considerations such as the ability of the administrator to place the PPD/TST, compliance of the patient to return for the second visit, and ability of the clinician to accurately read the PPD/TST. The total sensitivity and specificity of a test includes both the immunological and the programmatic characteristics and is defined as the ability of a test to provide for accurate diagnostic information regarding the absence or the presence of an infection.

The programmatic sensitivity of PPD/TST is affected by the subjectivity of interpretation of PPD/TST reactions. Traditionally, PPD reactions are under-read; 93% of 107 clinicians misread a known positive (Kendig, 1996). In this study the median reading was 10mm with 17% reading <10mm. Only 8 individuals read the induration as >15mm (Kendig, 1996). Programmatic sensitivity is further confounded by poor patient compliance with follow-up for reading of the PPD/TST.

Objective:

Optimally, a complete evaluation of a QuantiFERON-TB tuberculosis screening strategy into the military would include a rigorous cost-effectiveness analysis comparing QuantiFERON-TB to the current standard, PPD/TST. The

analysis would provide a tool by which one could determine the expected changes in effectiveness, as well as expected changes in the cost-saving ability of each screening strategy. Traditionally, the cost-effectiveness of a strategy would be determined by consideration of a cost-effectiveness ratio:

$$\frac{\sum_{i=1}^n (SP_{xi} + I_{xi})}{\text{effectiveness}_x} - \frac{\sum_{i=1}^n (SP_{yi} + I_{yi})}{\text{effectiveness}_y}$$

where:

SP= screening program costs

I= illness costs

and x and y represent different strategies.

Costs, considered in the numerator of the equation, include health care resources (cost of medical equipment for screening, cost of screening personnel, cost for treatment of infection, etc.), non-health care resources (transportation costs), and patient time (productivity time lost for screening, productivity lost for treatment, etc.) (Luce, 1996) (Figure 1). The measure of effectiveness in the denominator refers to changes in health. The definition of effectiveness will vary according to the goals of the program under evaluation. In the case of an analysis comparing tuberculosis screening strategies, effectiveness would be measured by prevented cases of tuberculosis or cases of tuberculosis receiving treatment. Examples of decision trees and the parameter estimates necessary to conduct a cost-effectiveness evaluation comparing PPD/TST to QuantiFERON-TB in the military are illustrated in Figure 2a and Figure 2b.

In the military the conditions and settings under which tuberculosis screening occur, as well as the operational needs of each program are complex. Valid and reliable event level data for imputation into a cost-effectiveness model for estimation of both the numerator and the denominator are lacking. Furthermore, data regarding the total sensitivity and specificity of QuantiFERON-TB and PPD/TST and data regarding the impact of the objective nature of placing and reading PPD/TST, including the compliance of patients to return to have the test read, are lacking. Through Delphi technique, attempts were made to collect data on event parameters, which would effect the cost and effectiveness of a

screening program (e.g., the probability that a PPD/TST is placed correctly). However, extreme ceiling and floor effects were observed (values clustered around 95% and 0%). Consequently, it is impossible to measure the probability of events associated with evaluation of a screening program with a high degree of accuracy. Parameter values could be estimated. However, evaluation of a set of parameters with wide confidence intervals would result in invalid conclusions. Furthermore, this report can not comment on the immunological sensitivity and specificity of PPD/TST or QuantiFERON-TB.

In the absence of evaluation data a rigorous cost-effectiveness analysis can not be conducted. Consequently, this analysis is limited to description of the current screening programs in the Army, the Navy (Marines will be considered under the auspices of the Navy), and the Air Force. Efforts are made to collect information on events, which would impact the programmatic sensitivity and specificity of PPD/TST. The consistency and validity with which PPD/TST results are recorded is also addressed. The potential for QuantiFERON-TB to improve the incremental cost-effectiveness of tuberculosis screening is discussed. The costs of screening related events associated with each strategy are additionally estimated.

The purpose of this report is not to evaluate the cost-effectiveness of QuantiFERON-TB but rather to discuss the expected influence of factors relating to tuberculosis screening on the cost-effectiveness ratio.

Methods:

Through a modified three stage Delphi technique, descriptive data was collected from individuals in the military with experience in tuberculosis control. Walter Reed Army Institute of Research (WRAIR) preventive medicine officers identified relevant military personnel for invitation to participate in the study. Senior officers in charge of tuberculosis screening activities in the Army, Navy and Air Force were targeted. To provide accounts of ground level experiences, effort was made to additionally include individuals with current field experience in tuberculosis control, as well as laboratory personnel and military researchers. All

named individuals were invited to participate in service specific focus groups (Stage 1). The purpose of the discussions was described as “an effort to provide information to develop a model with which to do an economic analysis comparing use of PPD with QuantiFERON-TB for tuberculosis testing”. While face-to-face formatted focus groups would improve the validity and reliability of the study, participating individuals reside across the country. Collection of individuals to a central site was cost prohibitive. Consequently, the focus groups were conducted via a telephone conference call. However, efforts were made to have individuals within reasonable traveling distance from one another (30 miles) to convene at the same location for the call. An outline of the focus group discussion (appendix b) was sent to invited participants two weeks prior to the first interview. The outline had three purposes: 1) to initiate discussions; 2) to allow senior officers to identify other individuals who may be appropriate to participate; and 3) to allow for collection of data to facilitate discussions on parameter estimations. The outline included the following domains: framing and background of current tuberculosis screening program, parameter estimation, and summary comments. The focus groups were conducted consistent with the structure of the outline. However, discussions proceeded in an open format. During the focus groups individuals with current involvement in evaluation of tuberculosis screening programs for each service were targeted for participation in Stage 2.

In Stage 2, individuals identified during Stage 1 were invited for small group or one-on-one discussions regarding ongoing analyses. When possible data were forwarded to study personnel to aid in completion of this report.

In Stage 3, all participating individuals, as well as individuals named too late to be included in the service specific focus groups were sent a questionnaire (appendix c). The questionnaire followed a format similar to the focus group discussion outline and was used to verify and serve as an imputation source for information provided during the focus group discussions in Stage 1, as well as provide additional preference data (appendix d).

Screening costs per individual screening event were estimated for the PPD/TST and the QuantiFERON-TB strategies. The Army training population was used as a conservative baseline estimate. Estimates of personnel time for placement and reading of the PPD/TST were developed during the Army Stage 1 focus group. Personnel costs were estimated from figures provided by the U.S. Army Training and Doctrine Command, Fort Sam Houston, TX. PPD/TST materials cost were provided during Stage 2 (CDR Wayne McBride, Preventive Medicine Program Manager, U.S. Navy Bureau of Medicine and Surgery; and COL Dana Bradshaw, Chief of Preventive Medicine, Air Force Medical Operations Agency, facsimile, December 6, 1999). The manufacturer (CSL Biosciences, Parkville, Victoria, Australia) provided cost and time estimates for QuantiFERON-TB. Estimates of laboratory time specific to military personnel may be available (MAJ. Rohit Katial, AFEB, February, 2000). However, these costs were not made available for this report. Supply costs for a blood draw were obtained from the published literature. When multiple estimates were obtained median values were used. The cost of laboratory technician time was estimated through adaptation of published accounts of technician time at the Johns Hopkins University. Other costs were derived from the published literature and adapted into U.S. 1998 dollars using the Consumer Price Index (Bureau of Labor Statistics, 1999). Industry specific index ratios were used when possible.

Tuberculosis Screening in the Military:

In October 1999, 15 military personnel representing the Army, Navy, and Air Force were invited to participate in the focus groups on tuberculosis screening (appendix a). Reserve representation was also included for each service. 80% (12/15) of those invited participated on an initial organizing telephone call. Four individuals were added for Stage 1 invitation, bringing the initial target group total to 19 individuals. Of these 68% (13/19) participated in the service specific focus groups. Four individuals participated in Stage 2 representing each of the three services and offered information beyond that

discussed in the focus groups. For Stage 3 participation, two individuals were added to the list of individuals who received the written questionnaire. A total of 11 individuals participated in Stage 3. Three individuals did not participate in any stage of the study or only participated in the first organizational conversation. The tuberculosis screening program of each service will be discussed below. Programmatic components expected to affect the total sensitivity and specificity of each tuberculosis screening strategy will be discussed for each service.

Cost for Screening Related Events

To estimate the cost of a screening event using either QuantiFERON-TB or PPD/TST would require measurement of a host of component costs, including:

- the cost of the screening tests (both PPD/TST and QuantiFERON-TB);
- costs of medical personnel and materials, for administration of the test or collection of the blood specimen (both PPD/TST and QuantiFERON-TB);
- lost productivity costs for the individual being screened for the time required to be screened (both PPD/TST and QuantiFERON-TB);
- transportation and processing costs for shipment of the blood specimen to a laboratory facility (QuantiFERON-TB);
- laboratory personnel and materials costs (QuantiFERON-TB);
- costs of medical personnel, for follow-up or reading of the PPD/TST (PPD/TST); and
- lost productivity costs for the individual being screened for the time required to have the PPD/TST read (PPD/TST).

Considerations such as cost of medical personnel time and lost productivity for time having a blood specimen drawn, or a PPD/TST placed and read will depend on the setting in which the screening occurs, the time requirements for screening and the rank (and responsibilities) of the individual being screened. For example, mass screening events are conducted in training settings where many individuals can be screened at once requiring minimal time. However, regular scheduled screening for individuals such as deployable units may require

independent clinic visits for each individual. The cost of the clinic appointment would consist of not only the medical costs of supplies and personnel but the time spent traveling to the clinic and time spent waiting once at the clinic for the individual being screened. Lost productivity time not only includes wages but non-quantifiable units such as time missed from training and the associated diminished skill building experiences due to decreased time spent developing the skills taught in training. This time can be thought of in terms of “lost productivity costs” or time which could be spent on another potentially valuable activity that is rather spent being screened.

Transportation and processing costs with regard to QuantiFERON-TB will depend on the proximity of the screening site to the laboratory. In some cases where the laboratory is located in the same building as the screening setting transportation costs will be minimal. However, in some settings (e.g., basic training) specimens would have to be transported to another location on the same base or another site.

Laboratory costs will depend on the salaries of the laboratory technicians (American Society of Clinical Pathologists (ASCP) board certification versus individual with Bachelor degree in biology). Additionally, the time required to complete the tasks associated with the QuantiFERON-TB will depend on the skill of the technicians (i.e., less skilled technicians would take longer to transfer specimens into the culture plates).

Estimated costs for screening events associated with the QuantiFERON-TB and the PPD/TST strategies in a basic training population are presented in Table 1.

Table 1: Costs of QuantiFERON-TB compared to Tuberculosis Skin Test (PPD- Mantoux)¹ based on screening in Basic Training Population²

Cost Component	QuantiFERON-TB (\$ per test)	TST (PPD-Mantoux) (\$ per test)
Test Cost	\$6.21 ³	\$0.56 ⁴
First Visit (personnel) ⁵	\$0.70 ⁶	\$0.37 ⁷
First Visit (lost productivity) ⁸	\$8.69 ⁹	\$8.69 ⁹
Specimen Transportation	\$0.22	\$0
Technician Cost	\$1.26 ¹⁰	\$0
Second Visit (personnel costs) ⁵	\$0	\$0.02 ¹¹
Second Visit (lost productivity) ⁸	\$0	\$8.69 ⁹
TOTAL per test	\$17.08	\$18.33

Using Army data in a training setting PPD/TST cost approximately \$18.33 per individual screening event, including test cost, medical personnel costs, materials, and lost opportunity. While QuantiFERON-TB cost an expected \$17.08 per individual screening event, including assay cost (materials and transportation), medical personnel costs, laboratory costs, and lost productivity. The incremental cost-savings would be \$1.25. These costs are not significantly different from one another. The cost of PPD/TST had a mean of \$0.31 ±\$0.25. Personnel costs are underestimated for both strategies. For example, in many settings PPD/TST results are entered on a personnel roster and later transcribed into individual medical records. The personnel costs associated with processing were not modeled in the cost estimate. In addition, a low, cost screening venue

¹ 1998 U.S. dollars, adjusted using the Consumer Price Index, Medical Laboratories, Independent Clinical Lab Services Component, and the General Medical, Outpatient Treatments components, 1999, Bureau of Labor Statistics.

² Costs estimated for Army personnel, assumed to be similar across the services.

³ Based on \$0.21 for collection supplies (Howell, in press) and \$6.00 for QuantiFERON-TB, (CSL Biosciences, Parkville, Australia, 1999).

⁴ Including administration supplies (\$0.18) and Tubersol or Aplisol (\$0.38).

⁵ The administration cost will vary significantly per screening site (e.g., mass screening in recruit population vs. TMC visit (\$56) other soldiers)

⁶ Based on 3 minutes of specialist E-3 time, (specialist E-3=\$14/hour, MAJ Hewitson, Preventive Medicine, January 13, 1999- labor costs).

⁷ Based on 3 minutes of E-3 time (E-3=\$7.40/hour, Defense Finance and Accounting Service, 1998, basic pay scale).

⁸ The opportunity cost will vary significantly across screening populations (e.g., training vs. artillery specialist).

⁹ Based on 30 minutes of soldier time (training day=\$139/day, U.S Army Training and Doctrine Command Headquarters, Fort Sam Houston, TX).

¹⁰ Based on 2.1 technician minutes (\$36.05/hour, including wage, benefits and overhead, Howell, 1998) for 215 tests per day.

¹¹ Based on .15 minutes of E-3 time for 200 reads in 30 minutes.

(i.e., a mass, recruit, screening event) was used in the cost model. Use of clinic time, where each individual has an independent clinic visit would dramatically effect the cost-saving ratio. For example, increasing the medical personnel and materials costs from 3 minutes in mass screening to that of a TMC visit (\$56), and adjusting the lost productivity time would increase the cost of the PPD/TST strategy to \$147.32 per screening event and the cost of QuantiFERON-TB to \$81.07, a difference of \$66.25. Changes in lost productivity of individuals being screened, comparing individuals with different wages and work responsibilities (e.g., chaplin versus a ammunicions technician), would dramatically affect the incremental cost-savings. For example, if a minimum wage (\$5.15) were used PPD/TST would cost \$6.09 and QuantiFERON-TB would cost \$10.96, a difference of \$4.87 per screening event.

Considering the range of estimates available the comparison values discussed in Table 1 can be thought of as a conservative baseline estimate designed to favor the standard (PPD/TST). Graph 1 indicates the relationship between the cost of QuantiFERON-TB and PPD/TST strategies as the cost of lost productivity ranges from \$5.15 per hour to \$24.00 per hour. The lost productivity cost threshold above which QuantiFERON-TB costs less than PPD/TST is approximately \$16.00 per hour. Graph 2 indicates the relationship between the cost of the QuantiFERON-TB and the PPD/TST strategies as the lost productivity cost varies, assuming a higher medical personnel and materials cost of \$56 per screening visit. Under these assumptions the cost of the QuantiFERON-TB strategy always costs less than the PPD/TST strategy. Removing the cost of transportation would only increase the cost-saving potential of a QuantiFERON-TB screening event over that experienced with a PPD/TST strategy. In the baseline case (training setting), doubling the laboratory costs per screening event makes the cost of the QuantiFERON-TB strategy equal to the PPD/TST strategy. In other settings, doubling the laboratory costs associated with QuantiFERON-TB would have minimal impact on the relationship between the two strategies.

Navy:

The Navy Tuberculosis Control Program is designed “to preserve the health of Naval personnel through the early identification and treatment of tuberculosis”. Currently, the Navy Tuberculosis Control Program directs that annual PPD screening be conducted on seven populations: 1) incoming recruits, 2) shipboard personnel 3) deployable units, 4) health care workers, 5) inmates and Naval Brigs staff, 6) personnel stationed at high risk overseas duty stations, and 7) individuals separating or retiring from the Navy. All other personnel receive screening every three years. This screening strategy holds for Navy, Marine Corps and Reserve personnel, BUMED/NAVMEDCOM regulations, Chapter 6224.1. Most of the skin testing occurs in branch clinics and in Naval Hospitals. The tuberculosis skin tests (PPD/TST) are placed and read by corpsmen. However, in operational settings (shipboard, overseas deployed locations, etc) various levels of personnel place the PPD/TST.

Recruit Population

Approximately 50,000 new recruits enter basic training at Great Lakes each year. This number has remained relatively stable over the past few years. The PPD/TST are placed during the first full day of basic training. Recruits are asked to return after 48 hours for the PPD/TST to be read. Corpsmen place and read the PPD/TST with preventive medicine oversight. The corpsmen receive introduction to tuberculosis screening in hospital corp school.¹² However, no specialty training in preventive medicine or laboratory services is undertaken. The corpsmen are instructed to read the induration rather than erythema and attempts to standardize reading protocol regardless of risk have been made ($\geq 10\text{mm}$ is considered reactive and an evaluation is required). All results are recorded using either a zero or a numeric indication of the induration in millimeters. Results are hand entered on a roster and later transcribed into individual medical records.

¹² Hospital corp school lasts a total of 4 months

Individuals with reactive tests are sent to preventive medicine for confirmation and a work-up, including chest x-ray. Prophylactic treatment is generally initiated. Individuals who have a documented past history of PPD reactivity are sent directly to preventive medicine for an x-ray. The PPD/TST is not placed for these individuals.

The Marine Corps screens approximately 21,000 recruits entering basic training each year. The tuberculosis screening program operates similar to that described for the Navy recruits.

The recruit screening occurs in mass where high numbers of PPD/TSTs are administered at the same time. A site observation by Army preventive medicine personnel at Great Lakes training base revealed that on one occasion weekend screening, the Recruit Division Commander had the recruits seated in rows of three with an aisle down the middle. The recruits extend their arms and the corpsmen read the PPD/TSTs while walking down the aisle. The Recruit Division Commander indicated that this arrangement was standard practice for PPD/TST reading.

Ship Board Population

In shipboard personnel the individuals are screened one-on-one by corpsmen. Individuals are asked to return to the screening clinic after 48 hours to have the test read. As with the recruits, a reaction 10mm is considered reactive and PPD reactive individuals are sent for a preventive medicine work-up. The results of shipboard personnel are recorded directly into the Shipboard Automated Medical System (SAMS), which maintains record of immunization and screening results. In the shipboard setting, there is less oversight by and access to preventive medicine physicians for evaluation and consultation for difficult to interpret results than in the training setting.

Deployable Units

Deployable units are evaluated on an annual basis to maintain medical readiness¹³. The evaluation includes screening, such as tuberculosis and HIV. Much of this screening occurs at branch clinics and at Naval hospitals and requires a routine clinic appointment. Positive tests require an emergency appointment for confirmation, which would be associated with a substantial screening cost.

Other

Medical personnel and inmates additionally receive annual screening. All other active duty personnel receive triennial screening at branch clinics and Naval hospitals. All personnel receive tuberculosis screening at separation from the Navy and the Marines as part of a departure battery of tests.

Comment

Navy participants believe that the Navy and Marine Corp are challenged more so than the Army and the Air Force due to the high number of screening sites and diversity of settings, which leads to difficulty in standardization of protocols. The parameters most likely to affect the cost-effectiveness of tuberculosis screening include, the placement and reading of test in terms of accuracy, timeliness and lost productivity cost, the rate of follow-up for PPD/TST readings, the ability of the results to be recorded in a structured and accessible format, and laboratory ease. Each of these components will be discussed below from the perspective of each setting.

Placement and Reading:

Participants expressed concerns with the subjective component of PPD/TST reading and interpretation. The corpsmen placing and reading the PPD/TSTs do not receive specialty training in tuberculosis screening and control.

¹³ Readiness- the preparedness of soldiers to be deployed at any time, to include absence of diseases that may interfere with job performance.

However, the preventive medicine staff participating in the focus groups believes the high volume of tests being placed and read each year in basic training rapidly leads to development of expertise. In the presence of a preventive medicine supervisor corpsmen are evaluated, difficulties are addressed and personnel with formal training are made available for consultation on difficult to interpret results. However, regardless of this oversight high variability of result interpretation is thought to exist. Efforts to standardize and provide high quality training for corpsmen placing and reading the PPD/TST are needed. One estimate placed the reading ability of the corpsmen at 85%.

During weekend reading events in recruits (as evidenced by the anecdotal experience noted at Great Lakes above) and in the field settings (e.g. ships and submarines) standard quality assurance and attention to detail is thought to wane. In field settings, one-on-one care is provided. However, there is less access to senior providers or physicians and less opportunity for consultation for questionable readings or interpretations. Passive efforts to monitor inadequate attention to detail are undertaken. For example, it is rare that a training company would have an absence of PPD reactors. When this occurs, the preventive medicine technicians observe screening activities for quality assurance. Often the training company has the PPD/TSTs re-placed and re-read. In non-deployable units, there is less concern for medical readiness than in operational units. Consequently, fewer efforts to ensure appropriate and timely screening are undertaken, theoretically decreasing the programmatic sensitivity and specificity of PPD/TST screening.

A recent review of one year of test results fueled concerns with over-interpretation of results. The review found a clustering of results around 10mm, 15mm, and 20mm. A high number of results were recorded as 10mm but were probably over estimated. Over all a tendency to error on the side of caution, where results were inappropriately classified as reactive, was observed (unpublished data, LCDR Ryan, Emerging Illness Division, December 14, 1999).

Outside of recruit populations concerns with the regularity of triennial screening were expressed. In this group, tests are often not administered on a regular schedule, potentially leaving many individuals unscreened.

The time required for PPD/TST screening was described as minimal for training populations, those screened at separation, and shipboard personnel. These events are conducted on either high volume of individuals at a time or are in captive populations (e.g. shipboard personnel only have to travel across the ship to receive screening). However, the lost productivity cost for screening in other populations (deployable units and other annual screening populations) could be substantial. The second visit for reading of the PPD/TST in some settings could require a couple of hours, including traveling time and clinic waiting time. Strong perceived advantages were expressed for a test, which requires only one health care visit.

Follow-up:¹⁴

The extent to which individuals return for a second visit to have the PPD/TST read varied by population. In the training, the shipboard, and the pre-deployment populations follow-up was described as good, due to presence of a captive audience (shipboard), efforts to assure medical readiness, and the presence of a well structured protocol (training). Evaluation of the SAMS data base indicated that 80% of those with PPD/TSTs placed return for the PPD/TST to be read (personnel communication, CDR Wayne McBride, Bureau of Medicine and Surgery, January 11, 2000). However, even a follow-up of 80% would negative affect the ability of the TB screening program to accurately identify infected individuals. In field settings a high number of tests that are placed are not read. Anecdotally, clinicians often tell patients if the PPD/TST reaction "doesn't look bad don't come back". In Reserve populations activities are commonly conducted on Saturday and Sunday. Consequently, after 48 hours the Reservists have returned home and must have their PPD/TST read at private

¹⁴ Follow-up here refers to the second screening visit in the PPD/TST strategy to read the PPD reactivity.

clinicians. The follow-up rate significantly affects the potential effectiveness of the PPD/TST strategy. With QuantiFERON-TB a follow-up visit is unnecessary.

Recording of Results:

Recording of the PPD/TST results in the Navy is considered strong. Active tracking is possible through SAMS immunization tracking element. However, in recruit populations results are recorded on a mass roster and transcribed by hand to individual records. Implementation of a QuantiFERON-TB tuberculosis screening strategy would facilitate recording of results through direct entry at the laboratory, improving accuracy of results and allowing for reminders to be sent, thus improving the timeliness of screening. Furthermore, this method has potential to save personnel costs through decreased time associated with manual entry of results into individual records. However, this strategy would require alterations to SAMS to reconfigure the data fields associated with tuberculosis screening. The SAMS is upgraded once or twice a year and alterations could be conducted during upgrades. While participants acknowledged a cost associated with the reconfiguration of SAMS, they believed that the cost would not be prohibitive.

Laboratory:

While the laboratory requirements for QuantiFERON-TB are minimal and commonly found in laboratories (consumables, incubator, ELISA reader) concerns with the limited feasibility associated with the presence of inadequately equipped laboratories in field environments. Furthermore, concerns were expressed with the handling and transportation of a biohazard specimen. The total cost of QuantiFERON-TB would include laboratory technician time, a cost not present for PPD/TST.

Immunological Characteristics of Screening Tests:

Several participants expressed a desire for further information on the sensitivity and specificity characteristics of QuantiFERON-TB. Furthermore, conflicting opinions on the performance ability of PPD/TST were expressed.

Some participants expressed concerns with the sensitivity of PPD/TST and cited the inability to use PPD/TST on individuals previously infected as a concern. Other participants perceived PPD/TST as a sensitive test.

Other:

In the Navy and Marines, tuberculosis screening requires scrupulous control. Missed cases in shipboard personnel could lead to widespread transmission during cruise activity (e.g. U.S.S Wasp experience, unpublished data, CDR W. McBride, 2000). Outbreaks would require expensive evaluation and evacuation of tuberculosis cases. QuantiFERON-TB has the potential to offer improved control over tuberculosis screening given improved total (immunological and programmatic) sensitivity and specificity compared to that of PPD/TST. However, while implementation of QuantiFERON-TB in the Navy and Marines could provide benefit over PPD/TST in some settings, Navy participants expressed a desire for further information evaluating the immunological characteristics of QuantiFERON-TB. While imperfect, participants described PPD/TST as a simple screening test with a well accepted standard of use and a well documented extensive history. PPD/TST is perceived as simple to perform and inexpensive in materials costs.

Army:

Currently, the Army conducts tuberculosis screening on six general populations: 1) individuals entering the Army, 2) deployed units, 3) deployable units, 4) special forces, 5) inmates and personnel of jails, and 6) hospital personnel. Active duty personnel not deploying ordinarily receive screening every 5 years as part of a periodic physical exam, unless one has been administered within the past 6 months. Screening is conducted consistent with Centers for Disease Control guidelines and Army Preventive Medicine Regulations (Army Regulation 40-5).

Populations Entering the Army

Similar to the Navy, Army recruits (approximately 40,000 individuals per year) are tested in large groups early in the basic training process. All individuals entering active duty for 30 days or more are required to be screened for tuberculosis. The PPD/TSTs are placed and read by non-specialist enlisted personnel (E-2 or E-3) supervised by an E-6. The PPD/TSTs are batched in advance and are administered on large numbers of individuals at a time. The PPD/TST placement and reading events take an estimated 30 minutes each. Results are documented by hand on individual SF-601 forms, immunization component. Individuals with PPD reactions (induration 10mm) are sent to preventive medicine for a work-up (duration 1 hour), conducted by either a registered nurse or a community health nurse. The individual is then referred to a physician to rule out active disease and evaluate for INH. Newly entering Reservists are screened for tuberculosis during basic training (approximately 20,000 per year). Individuals with documentation of past PPD reactivity are exempt from further screening with PPD/TST.

Deployable Units

All deployable units should be tested pre-deployment. At some posts deployable units are tested annually as part of the Soldier Readiness Program. In this population PPD/TSTs are placed and read in mass screening events. The screening protocol varies by site and deployment assignment. Individuals travelling out of the continental US on Permanent Change of Station orders are required to be screened within 3 months of departure. Individuals returning from deployment are advised to receive testing within 2 months of their return, including Reservists. If screening is not conducted post-deployment individuals are required to be screened within 2 weeks of arrival at their next assignment. Reservists returning from overseas have PPD/TSTs placed at the de-mobilization site. These individuals are instructed to receive a follow-up PPD/TST after 90

days. Individuals with documentation of past PPD reactivity are exempt from further screening with PPD/TST.

Other

Hospital personnel (e.g., WRAMC, 7,000), inmate populations, and special operations units (approximately 21,000 individuals per year, including deployable units) receive annual screening. Record of PPD reactions is recorded on SF-601 immunization sheets.

Comment

Army participants cited similar concerns to Navy participants described above.

Placement and Reading:

Army participants expressed concerns with the variability in PPD/TST technique including, reading and interpretation of induration size due to poor training of personnel administering the test. Passive efforts to monitor PPD/TST quality are undertaken similar to that of the Navy. Difficulties assuring PPD/TST screening pre-deployment have been observed (e.g., Somalia) (OTSG, 1994). Participants questioned the timeliness with which soldiers received screening, especially in Reserve populations. From May to July 1999, of 116 Special Operation Reservists requiring testing only 34% (40/116) received screening (MAJ William Corr, US Army Special Operations Command, facsimile transmission, November 9, 1999). An estimated 10% of Reserve populations returning from deployment receive repeat tests after 90 days as recommended. Furthermore, granting of leave following long deployments complicates follow-up schedules for reading of PPD/TST results (Shanawani, 1998).

The time required for PPD/TST screening was described as minimal for training populations, where the screening event is programmed into the training schedule and is not particularly disruptive to training events. In the training

setting, time for the placement visit and time for the second visit for reading of the PPD/TST was estimated as 30 minutes, regardless of mass placement and mass reading structures. The time costs due to lost productivity associated with a screening event in other populations was higher due to time not worked to attend the clinic.

Follow-up:

The extent to which individuals return for a second visit varied by population. In the training populations, patient compliance with follow-up visits to read the PPD/TST was described as good. However, in health care settings only an estimated 30% of individuals screened return to have the PPD/TSTs read if the patient initiates the follow-up visit. If a call back system is implemented an estimate 70% return. In one analysis, 16% of those that were placed were never read (Parkinson, 1991). Similarly, concern was expressed with the proportion of Reservists who have the PPD/TST placed and then read at a physicians office once returning to civilian life. Concern was also expressed with the cost, due to lost productivity associated with a clinic visit for each individual for reading of the PPD/TST. The requirement of only one visit for tuberculosis screening was cited as a significant strength of QuantiFERON-TB.

Recording of Results:

As opposed to the situation in the Navy, in the Army documentation of PPD/TST results is considered weak. Virtually no documentation to 30% documentation of negative PPD reactions in pre- and post-deploying individuals was estimated. Individuals returning from overseas are expected to receive screening within 2 months of return. However, poor recording systems create difficulties in determining who received screening and who did not. Documentation of PPD reactions in Reservists is not undertaken. Recent review of PPD/TST result records indicated a high level of improper entries where PPD reaction was coded as "positive" or "negative" without a measure of induration (Popper, 1991). Blatant miscoding of PPD reactive individuals with negative results has been observed (Sowell, 1970). Participants expressed satisfaction

with the ability of a QuantiFERON-TB strategy to allow for quantification and improved documentation of results.

Laboratory:

As with Navy participants, Army participants cited concerns with the ability of laboratories to handle QuantiFERON-TB testing in terms of laboratory workload and equipment. Additionally, funding for a QuantiFERON-TB strategy was questioned. In areas with low numbers of tests, the availability of laboratory equipment was expressed as a concern. Concern was expressed with the 12 hour holding limitation on blood specimen. Participants cited concern with the cost of QuantiFERON-TB relative to PPD/TST.

Immunological Characteristics of Screening Tests:

Several participants expressed concerns with the sensitivity and specificity of PPD/TST, while others expressed satisfaction with the specificity of PPD/TST. Other individuals cited the increased sensitivity of QuantiFERON-TB and the ability of QuantiFERON-TB to differentiate between MAC and *M. tuberculosis* as strengths.

Other:

As in all settings false-positive results can incur high costs. In 1996, at Fort Leavenworth a conversion rate of 2.6% was observed in inmates and personnel. An extensive epidemiological and retrospective contact evaluation was undertaken to identify the source of the potential epidemic. All converters underwent chest x-ray and showed no evidence of active disease. The high converter rate was credited to high false positivity associated with the PPD/TST stock (MSMR, 1996). Improvement in test quality would dramatically improve medical and evacuation costs, as well as the cost of epidemiological evaluations associated with false-positive results. Army participants expressed a familiarity with PPD/TST, facility of performance, low cost, and acceptability to soldiers as strengths of the PPD/TST. However, individuals participating in Stage 3

universally expressed a desire for QuantiFERON-TB to be used in conjunction with the PPD/TST strategy or replace the PPD/TST. Recommendation was made for consultation of the individuals who conduct the screening event (i.e., placement and reading of test or blood draw).

Air Force:

The Air Force tuberculosis screening program is primarily concerned with preventing the occurrence of an active case of tuberculosis. The secondary goal of the program is to prevent transmission. Screening is conducted (on approximately 255,000 beneficiaries per year) consistent with CDC guidelines and the Air Force Instruction (AFI) 48-115. Screening occurs in four general populations, the first three of which are subsets of the active duty population,: 1) at entry to the Air Force, 2) deployable commands, 3) hospital personnel, and 4) non-active duty exposed to individuals with presumed/confirmed TB, working in environments at high-risk for TB or moving with their active duty sponsor to overseas locations.

Populations Entering the Air Force

Similar to the other services, new Air Force accessions, including recruits, new academy accessions and medical students are screened at entry to the Air Force (approximately 35,000 individuals per year). The PPD/TSTs are placed and read by enlisted personnel (E-3). Enlisted personnel administering the PPD/TST primarily receive training at the Wilford Hall Medical Center, Allergy and Immunology program. Some personnel attend the Walter Reed Army Medical Center (WRAMC) annual re-fresher training depending on base location. An E-6 would be required for a blood draw in the QuantiFERON-TB strategy. Higher level personnel (e.g., preventive medicine technicians) do not supervise junior enlisted personnel in accession settings during screening activities, as was reported in other services. Results are recorded in the Military Immunization Tracking System (MITS). The measurement of the PPD/TST reaction is recorded in this system in millimeters (mm). Positive reactors are additionally recorded in

the Air Force Reportable Events Surveillance System (AFRESS). Individuals with PPD reactions (induration \geq 10mm) are sent to Aerospace Medicine for a work-up, including chest x-ray and initiation of a six-month course of Isoniazid. Individuals with a documented history of PPD reactivity are exempt from future PPD/TST screening.

Deployable Commands

Members of the Air Mobility Command (AMC) receive annual screening for tuberculosis. However, most commands (Air Force One) have biennial screening schedules. Some bases have guidelines for "hot mobility"¹⁵ (Andrews Air Force Base). The number of PPD/TST placed and read each year depends on the deployment schedule. Approximately 16,000 individuals are deployed each month. A decreasing number of personnel will probably lead to a decline in total number of PPD/TSTs conducted each year.

Most members of deployable commands receive placement and reading of the PPD/TST at immunization clinics. If the patient does not comply with follow-up for reading of PPD reactivity the screening event is considered non-successful and the individual requires another test. Results are recorded in the MITS. Positive reactors are additionally recorded in the AFRES. If individuals are deployed without a current screening event (defined as within the past 12 months), the PPD/TST is placed at time of deployment and read upon arrival at the deployment site. Short notice mobility commands often have a high number of individuals with PPD/TST placed at time of departure.

Upon return from deployment all individuals receive an evaluation from public health. Post-deployment evaluation allows for documentation of possible exposures. Individuals with any possible exposures or concerns are referred to the flight surgeon. Individuals with a documented history of PPD reactivity are exempt from future PPD/TST screening.

¹⁵ hot mobility = short notice deployment individuals

Other Active Duty

All active duty Air Force personnel receive annual preventive health assessments (PHAs) to assure that the individual is "worldwide qualified". The physical exam section (PES) at each base administers PHAs. During the PHA all immunization and screening records are reviewed to assure currency. Individuals missing immunizations or past due on screening are referred to the immunization clinic on the base. Currently, mechanism of follow-up to assure compliance with referral does not exist. However, this depends on the individual carrying out the PHA. At some bases follow-up will be conducted even in the absence of standard follow-up protocols. At five year intervals, a physician conducts a complete physical exam and all outdated immunization and screening events are administered. Occupational health exams are also conducted on personnel in high- risk occupational settings. Results are recorded in the MITS. Positive reactors are recorded in the AFRESS. If the individual does not return for follow-up the screened event is not recorded. In the absence of a concrete result personnel require repeat screening.

Some bases with high numbers of individuals on mobility will actively screen all individuals each year (as opposed to relying on PHA and five year exams, as described above). However, this practice is not Air Force wide and many individuals receive biennial screening. Individuals with a documented history of PPD reactivity are exempt from future PPD/TST screening.

Other

As in the Army and the Navy, Air Force health care personnel receive a PPD/TST each year.

Comment

Air Force participants cited concerns similar to those described above.

Placement and Reading:

In general variability in reading skills and the subjective nature of interpretation of the PPD/TST was cited as a concern for many participants. A recent outbreak investigation at Ellsworth Air Force Base (EAFB) identified use of incorrect technique in reading the PPD/TST (Neuhauser, 2000). Upon observation, researchers determined that the immunization technicians reading the PPD/TST were measuring longitudinal, as well as transverse PPD reactions. The larger of the two was used for result determination. Current CDC guidelines and AFI 48-115 (Tuberculosis Detection and Control Program) recommend only measuring transversely. The researchers surmised that the practice of dual readings was responsible for an increase in the incidence of false positive results. Evaluation of screening practices at Ellsworth indicated moderate inter-observer coefficients (0.78-0.86) of the PPD/TST reaction (Neuhauser, 2000).

However, The Air Force Health Protection and Surveillance Branch is currently conducting a case-control study to establish risk stratification models. This Branch may also conduct a service specific decision analysis and cost-effectiveness analysis to address this issue.

The PHA, including the five year physicals have contributed to individuals receiving PPD/TST screening. In commands that receive screening on two year schedules, high numbers of individuals will lack a current screening event in the case of short notice deployment. Logistical concerns, such as the ability to transmit test results in the QuantiFERON-TB strategy to the field, were expressed. The invasive nature of both PPD/TST ("needle in arm") and QuantiFERON-TB ("blood draw") were reported as a disadvantage of both techniques.

Follow-up:

Approximately, 70 to 85% of individuals receiving PPD/TST screens return to have the test read. However, the rate of return for follow-up differs per population. The need for the patient to return for a reading of the PPD/TST and the time associated with the follow-up visit was cited as a concern for many participants. In the Air Force PPD/TSTs are not placed on Thursday or Friday

(preceding a Monday holiday) since PPDs are generally not read on the weekend. If an individual does not comply with follow-up to have the PPD reaction interpreted, the test result is recorded as “not read” and the screening is repeated. This practice can be particularly time consuming and expensive, costing an extra visit and lost productivity for placement of the PPD/TST and another for reading of the TST.

Recording of Results:

Documentation of PPD/TST results into MITS and AFRESS is described as good. Failure to follow-up leads to lower documentation.

Laboratory:

The feasibility of QuantiFERON-TB testing in field settings (deployments) was questioned. Training for clinicians and laboratory technicians was cited as a concern with regard to implementation of a QuantiFERON-TB strategy. The ability to potentially combine QuantiFERON-TB with other blood tests was reported as an advantage.

Immunological Characteristics of Screening Tests:

Air Force respondents in Stage 3, universally questioned the adequacy of the specificity of both strategies, as well as the probability of disease following a positive test result. A desire for further information on the immunological sensitivity and specificity for QuantiFERON-TB was expressed. The impact of risk categories on use of either test was questioned. Decreased cross-reactivity with QuantiFERON-TB was cited as an advantage. Inability to interpret discordance between QuantiFERON-TB and PPD/TST in evaluations of high risk populations was expressed as a concern.

Other:

Air Force participants expressed a familiarity with PPD/TST, satisfaction with evaluation of PPD/TST, facility of performance (especially in field settings), and satisfaction with low cost. Concern with inclusion of all costs in evaluation of

tuberculosis screening was expressed. Confusion with how to handle individuals who revert to negative was cited as a concern¹⁶. Participants requested intensive training in the form of peer-reviewed literature, newsletters, training courses (particularly for the public health, Air Force, aerospace medicine, and flight medicine communities). Air Force personnel questioned the immunological sensitivity and specificity of QuantiFERON-TB but expressed a desire for standardization of screening test interpretations and improved risk category guidelines.

Discussion:

While the data evaluating the immunological sensitivity and specificity of QuantiFERON-TB are incomplete QuantiFERON-TB offers practical advantages over PPD/TST. Consequently, a QuantiFERON-TB strategy could potentially improve the incremental cost-effectiveness of tuberculosis screening.

The costs presented in Table 1 are based on a training population, which represents a conservative comparison between PPD/TST and QuantiFERON-TB. In the training setting the lowest amount of time is associated with a PPD/TST screening event. However, in other settings where independent clinic visits are required for each individual the QuantiFERON-TB would require the least amount of time. The cost of lost productivity will vary significantly depending on professional characteristics of the individual being screened. The training population lost productivity cost includes supplies and salaries associated with instruction, site and service support and housing costs. In other settings lost productivity costs would include only salary for lost productivity time. As such, the lost training cost may not accurately represent those in other settings. The training cost breaks down into approximately \$17.00 per hour. This represents the mid range of salary for Army personnel. Other scenarios would exist with a variety of screening costs and lost productivity costs. These costs would vary per branch of the military, setting and individual being screened.

¹⁶ As noted above, individuals with a history of PPD reactivity are exempt from future PPD/TST

The cost estimates presented in Table 1 should be interpreted with caution. These costs represent lower bound estimates of screening related costs and represent only a small portion of the total costs associated with each strategy. These costs may not be generalizable across all services. The total costs associated with each strategy would include medical costs associated with the tuberculosis control program, as well as the screening event related costs. The model presented is meant to stimulate discussions on the expected influence of factors relating to tuberculosis screening that would impact the cost-effectiveness ratio.

Differences in the immunological and programmatic sensitivity and specificity between PPD/TST and QuantiFERON-TB would lead to different proportions of individuals receiving preventive medicine work-ups and treatment, as well as different future costs of missed infections and tuberculosis cases. These costs were not estimated in this report due to a lack of valid and reliable data. However, the implications of practical differences between the two strategies have been discussed qualitatively. The QuantiFERON-TB test requires a single 10ml blood draw; a technique which demands less training than that associated with the PPD/TST technique. Often blood is being drawn for other purposes (e.g., HIV screening). Consequently, a QuantiFERON-TB strategy would have lower personnel training costs than would a PPD/TST strategy. The QuantiFERON-TB assay costs more than the materials for PPD/TST. In addition, the technical costs associated with a QuantiFERON-TB strategy, beyond clinic staff, would include laboratory equipment and laboratory staff, requirements not present in a PPD/TST strategy. These costs would increase the direct costs associated with QuantiFERON-TB. It should be noted that for established serology and pathology laboratories (i.e., those with BioHazard hood, EIA plate washer and reader, and incubator) inclusion of QuantiFERON-TB in the battery of screening tests conducted on individuals would require very little additional investment, beyond that required to train laboratory personnel. However, QuantiFERON-TB does not require a second

screening and are sent directly for chest x-ray.

visit for reading the test results, obviating the need for a clinic visit in some settings. This cost can be \$56 for a Troop Medical Clinic visit (Howell, 1999). Additionally, QuantiFERON-TB decreases the time away from training or duty (lost productivity) for screening services resulting in lower lost productivity costs. QuantiFERON-TB requires transportation of an additional biohazard specimen, which would require processing once at the laboratory. However, the specimen would most likely be transported with already collected specimen, representing a very small additional cost per specimen. Consequently, while the per test assay costs of QuantiFERON-TB may be higher than PPD/TST, the total variable costs associated with the QuantiFERON-TB strategy may be lower than those associated with the PPD/TST due to lower clinic costs and lower lost productivity costs.

As noted, in some settings there exists a low return rate for the second visit in the PPD/TST strategy (e.g., Army Reserve populations). Consequently, there is potential for individuals with PPD reactivity to remain unidentified, incurring medical costs in the future. Additionally, individuals with negative results are not documented. In these scenarios, placement of the PPD/TST provides no clinical benefit, decreasing the potential effectiveness and increasing the cost of the PPD/TST strategy. QuantiFERON-TB has potential to improve this situation.

As was indicated in the discussions with military personnel, record keeping of the screening event, as well as the incidence of negative PPD/TST reactions is less than optimal. Often, results are not indicated in individual medical records and the test is re-administered, incurring additional cost.

Current data, though incomplete, indicate an equivalent immunological sensitivity and specificity of QuantiFERON-TB compared to PPD/TST. It is expected that the sensitivity of QuantiFERON-TB may be higher than PPD/TST. In several studies, concern over the specificity of QuantiFERON-TB was raised (Converse, 1997; Kimura, 1999). However, the specificity of QuantiFERON-TB may be higher in low to moderate risk populations than in the high risk populations considered, due to lower exposure rates to agents which may cause

cross reactivity (Converse, 1997). Equivalent or improved immunological sensitivity and specificity of QuantiFERON-TB would result in a higher probability of individuals accurately receiving care thus, increasing the effectiveness of a QuantiFERON-TB strategy and decreasing costs through prevention of unnecessary preventive medicine work-ups and therapy.

As noted in the Air Force case study, the subjectivity of the PPD/TST could lead to increased medical work-ups and costly epidemiological studies. This could be avoided through use of a screening test with a more objective interpretation of results.

For established serology and pathology laboratories introduction of QuantiFERON-TB would require few additional costs beyond personnel training. Furthermore, negotiations with the manufacturers of QuantiFERON-TB may allow for decreased costs of the assay when purchased in high volume. However, regardless of this potential cost-effectiveness, evaluation of the immunological sensitivity and specificity of QuantiFERON-TB, once completed, requires wider dissemination.

A majority of participants in Phase 3 indicated a desire for the PPD/TST program to be replaced or at least supplemented with a less subjective screening test. Guidance from national standards for public health practices (CDC, pulmonary/infectious disease specialty associations) may clarify understanding of test characteristics and improve provider and specialist acceptability. A U.S. Preventive Services Task Force review and evidence based evaluation could lead to greater confidence with a QuantiFERON-TB strategy. In settings where the PPD/TST program appears to be working well, maintenance of the PPD/TST strategy should be considered (recruit populations, incarcerated individuals, hospital personnel). However, training of personnel placing and reading the PPD/TST results should be improved, as should education on the immunological sensitivity and specificity of both PPD/TST and QuantiFERON-TB. In other settings (reserve populations, pre- and post-deployment screening, triennial) the practical advantages of QuantiFERON-TB are substantial. Circulation of educational materials and presentation of data by individuals independent of

QuantiFERON-TB manufacturers (e.g., individuals with experience in QuantiFERON-TB trials) may improve acceptability. Development and distribution of policy guidelines, as well as educational materials for the use of QuantiFERON-TB are necessary. Conduct of studies designed to quantitatively evaluate the programmatic effectiveness of PPD/TST and QuantiFERON-TB are necessary to fully evaluate the potential incremental cost-effectiveness provided by implementation of a QuantiFERON-TB strategy.

While the lack of data prohibits a rigorous cost-effectiveness analysis, this study found that a QuantiFERON-TB strategy offers practical advantages over a PPD/TST strategy. The decreased direct costs associated with improved practical efficiency associated with QuantiFERON-TB should provide benefit over a PPD/TST strategy to the military. However, use of QuantiFERON-TB may offer higher practical benefit in some settings than others (e.g., reserve populations, pre- and post-deployment). Branch and setting specific parameters should be considered to allow for tailoring of a cost-saving and effective tuberculosis prevention and control program.

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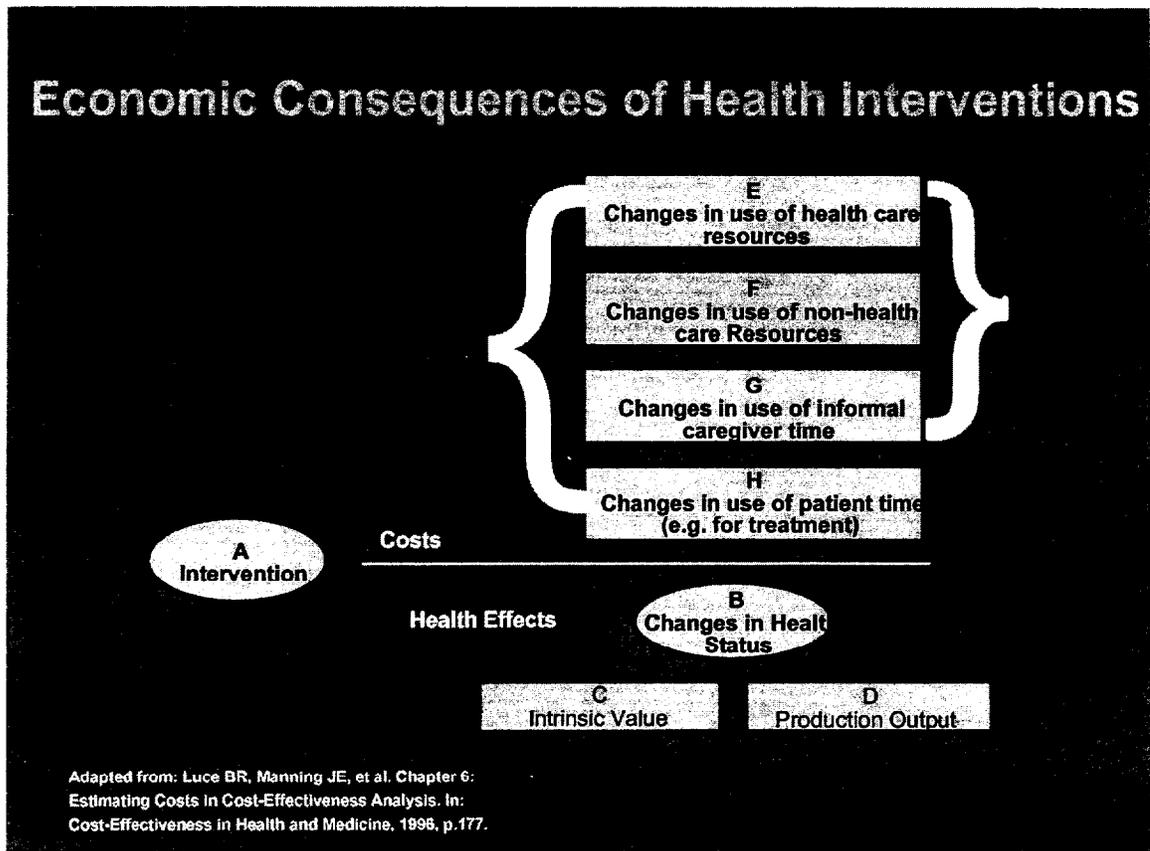
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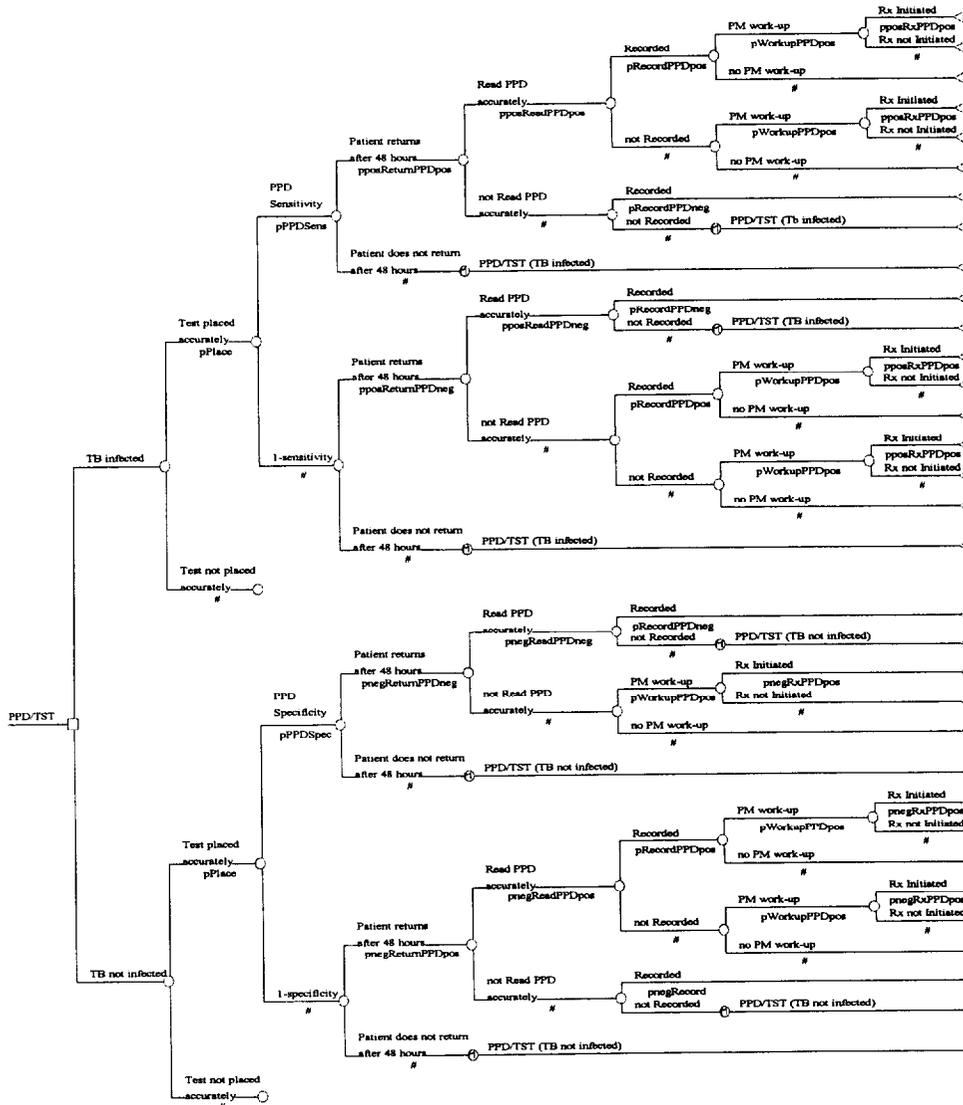
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Figure 1: Economic Consequences of Health Interventions



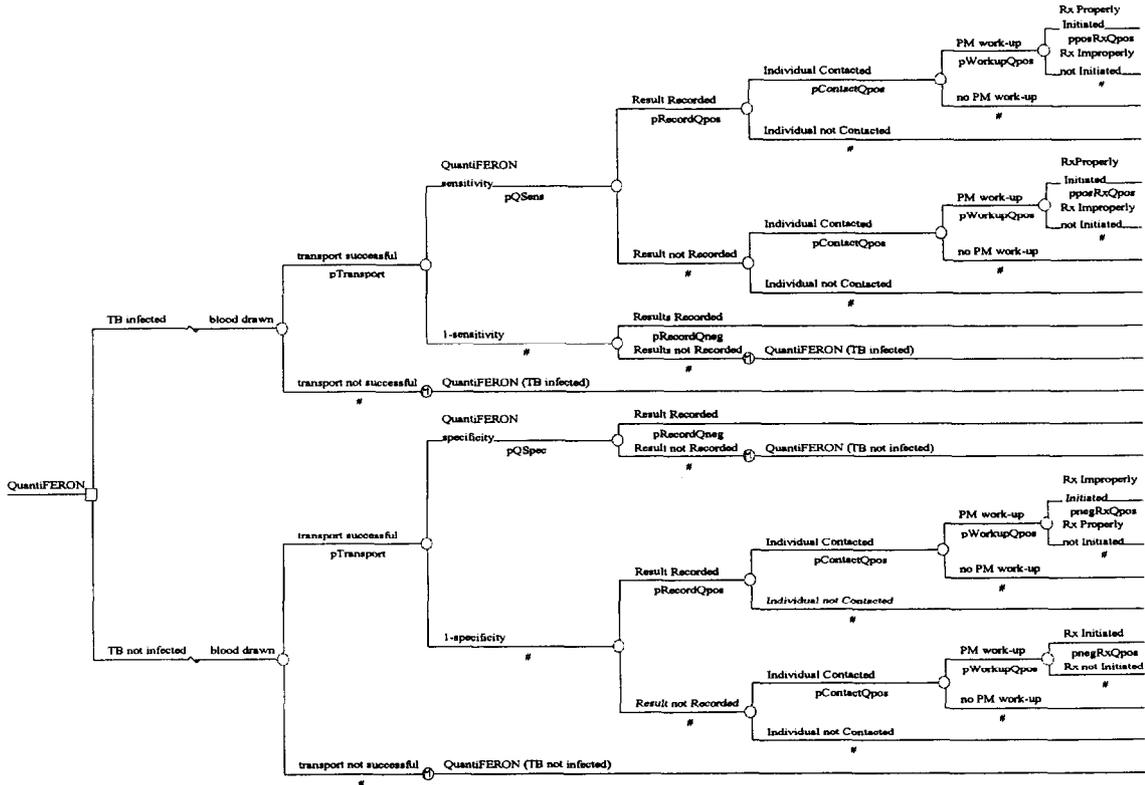
This figure represents the costs and benefits that are included in estimation of a cost-effectiveness ratio. An intervention requires resources such as a medical personnel to administer a test and laboratory personnel to process the clinical specimen (Box E). Furthermore, transportation and lost productivity costs in terms of lost training time associated with a screening event should be considered (Box F and Box H). If special care is required where family members (informal care-givers) require time off from work or away from leisure activities should also be considered (Box G). The effectiveness of the intervention can be measured in terms of health effects, such as cases of tuberculosis treated or prevented transmission of a case of tuberculosis or even improved quality of life (Box B). The improved health state will be associated with prevented medical costs (Box C) as well as altered productivity associated with improved health or prevented disease (Box D). While inclusion of all of these costs is not necessary if the societal perspective is assumed they will be estimated in a sound cost-benefit analysis.

Figure 2a: Simple Decision Tree: illustration of considerations necessary for cost-effectiveness analysis (PPD/TST)



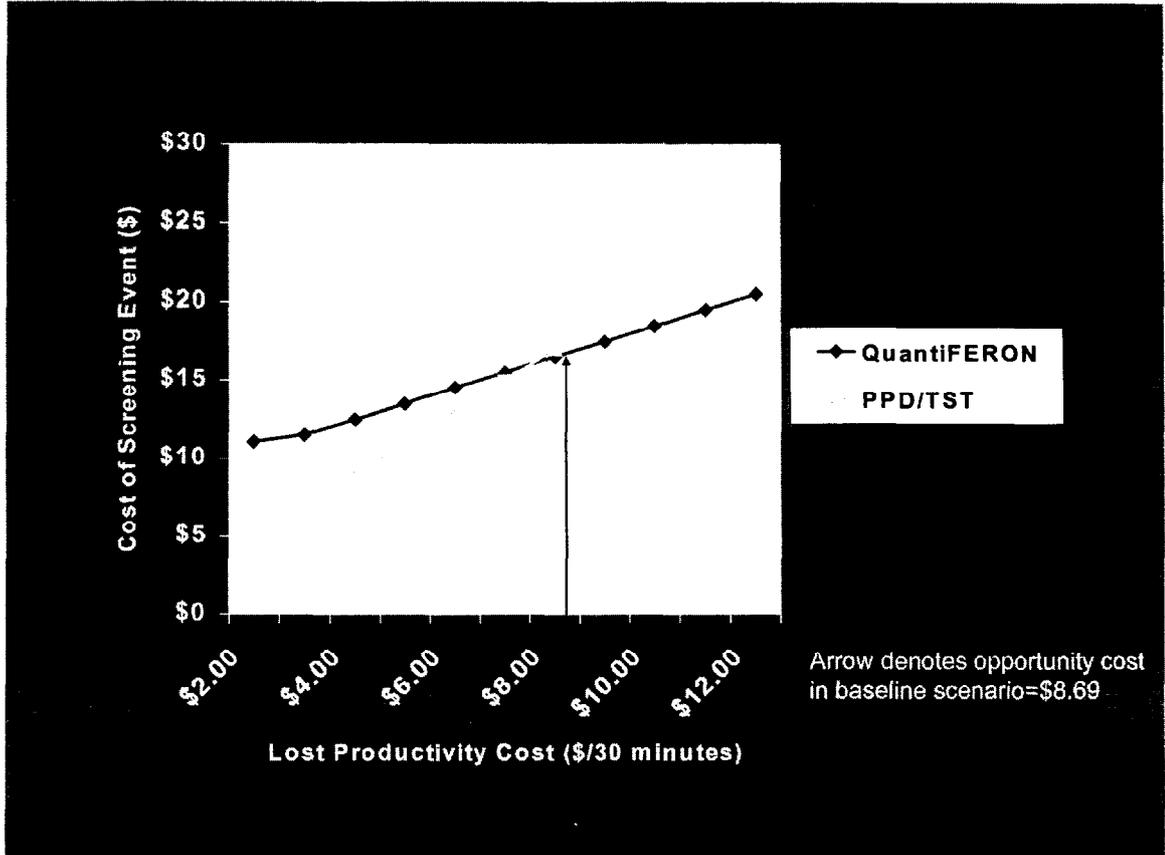
The tree is read from the left to the right. Each pathway represented a series of events that may occur with the screening program. Each branch in the decision tree represents an event associated with screening. Nodes denoted with a circle represent probability events. Nodes represented with a triangle are end nodes and are associated with a specific health event (prevented or non-prevented disease). The end nodes for each strategy are compared to assess the costs and effectiveness values associated with each strategy.

Figure 2b: Simple Decision Tree: illustration of considerations necessary for cost-effectiveness analysis (QuantiFERON-TB)



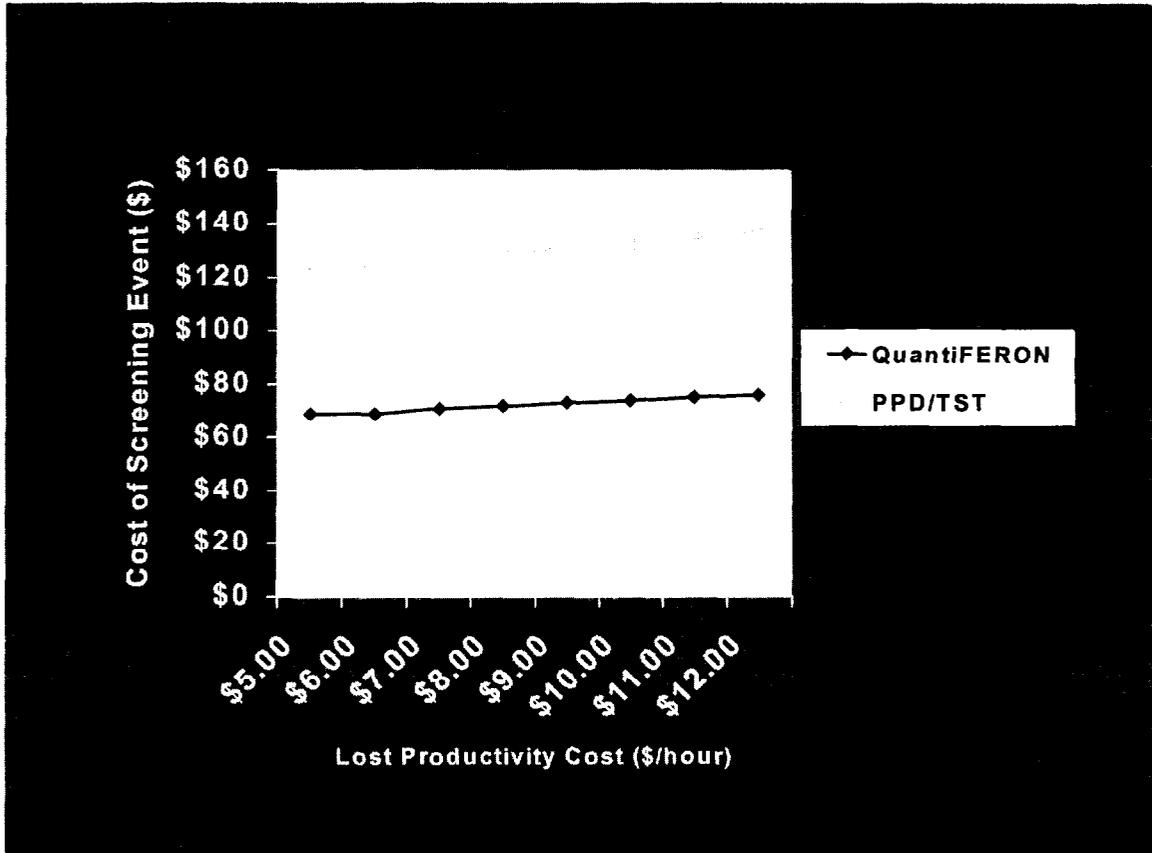
The tree is read from the left to the right. Each pathway represented a series of events that may occur with the screening program. Each branch in the decision tree represents an event associated with screening. Nodes denoted with a circle represent probability events. Nodes represented with a triangle are end nodes and are associated with a specific health event (prevented or non-prevented disease). The end nodes for each strategy are compared to assess the costs and effectiveness values associated with each strategy.

Figure 3: Cost of Screening Event as Lost Productivity cost varies



The x-axis represents varying lost productivity values, lost wages or missed training, from \$5.15 per hours to \$24.00 per hour assuming the screening program characteristics expected in an Army basic training setting. As the cost of lost productivity increases the relative cost of a screening event associated with QuantiFERON-TB costs less than that associated with PPD/TST, represented by the values on the y-axis. At hour costs over \$16.00 QuantiFERON-TB costs less than PPD/TST per screening event.

Figure 4: Cost of Screening Event as lost productivity cost varies, assuming a TMC visit for screening at a cost of \$56 per visit



The x-axis represents varying lost productivity values, lost wages or missed training, from \$5.15 per hours to \$24.00 per hour assuming a screening event clinic cost of \$56, as would be experienced for a Troop Medical Clinic visit. At high clinic costs, as opposed to the cost of personnel to administer mass screening tests, the QuantiFERON-TB always costs less than the PPD/TST regardless of the lost productivity cost for time away from service tasks.

Appendix A: List of Initial Participants Selected by Preventive Medicine Officers at Walter Reed Army Institute of Research (WRAIR)

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Appendix B: Stage 1 Memo of Outline for Focus Groups Initially Circulated to Participants on October 8, 1999 and November 5, 1999

To: Maj. Lisa Keep (for transmission)

From: M. Rene Howell

Date:

Re: Tuberculosis cost-effectiveness model: questions for consideration

Below please find a set of questions to use in considering the military advisory team for the tuberculosis cost-effectiveness analysis. This list is preliminary.

Framing and Background:

1. Description of the current tuberculosis program (including FORMAL as well as 'reality' protocols—it is important that I know what is supposed to be happening, as well as what really happens).
2. Who is screened.
3. Site of screening (e.g., IET, pre-deployment physical, etc.).
4. Objectives of tuberculosis control program.
5. Areas of the current program which need improvement (e.g., recording of results, accuracy of reads, etc.).
6. Description of the logistics of screening (e.g., who would place the test—specialist E-3?; who would read the test?).
7. Capabilities of current laboratory system to integrate QuantiFERON-TB testing results.

Parameter Estimates:

1. Estimate of rate at which individuals return for read.
2. Estimate of accuracy of reading the PPD results.
3. Time requirements for screening visit.
4. Treatment regime.
5. Clinic requirements for read or treatment.
6. Personnel costs
7. Storage of screening test
8. Costs of PPD (test, materials).

Summary:

1. Would you like to see QuantiFERON-TB replace the current system? Why or why not? (another way of getting at the same as 5. but more directed. Helps to direct what the objective of the CEA should be).

Appendix C: Survey Distributed During Stage 3

QuantiFERON® TB Survey: U.S. Military

Purpose of the Survey

The purpose of this survey is to allow CSL to plan to meet the needs of various services of the US Military in using the QuantiFERON® TB test for tuberculosis infection. All information in this survey will be treated confidentially and will only be used by CSL and the US Military for internal planning and discussion purposes.

This information will be considered as the opinion of the individual completing the survey and although it will help in making estimates for production planning, it will not be used to set forecasts nor will it be bound to any future supply discussions or contracts with any service of the US military or any branch of the US Government.

Once the results are available I will share all information with participants in the survey or any other interested parties in the US Military.

Instructions for completing the survey

The questions are straightforward and mostly pertain to current TB control programs in the Military.

- Simply insert answers in the survey table under the column "Answers".
- If a question is not applicable to your situation please insert "NA".
- If you cannot answer a question for any reason please insert "CA".
- Please attempt to give an accurate number or estimate. Insert a range of numbers if appropriate
- We have asked you to make some estimates and provide the following assumptions to assist in this process.

Assumptions for answering questions:

1. The QuantiFERON® TB test uses a single blood sample to test for TB infection, replacing the need for the Tuberculin Skin Test.
 2. The QuantiFERON® TB *in vitro* diagnostic test will be approved by the FDA for use in screening for TB infection in adults in mid-2000.
 3. The QuantiFERON® TB test is equivalent in efficacy to the Tuberculin Skin Test for screening of TB infection in adults.
 4. The QuantiFERON® TB test will be shown to be at least equivalent to the Tuberculin Skin Test in cost analysis and cost-effectiveness analysis for screening of TB infection in adults.
- Return the survey by email or fax to Paul Walton. Contact Paul if you have any questions about the survey:

Paul Walton Ph.D.
Snr. VP, Diagnostics
CSL US Inc.
13804 W 107th St
Lenexa KS 66215
Phone (913) 338 0373

QuantIFERON® TB Survey: US Military

Questions	Answers
Part A: Your details:	
1) Your Name?	1)
2) Your Title?	2)
3) Your Mailing Address?	3)
Part B: Your TB Control Program:	
4) What is your responsibility for TB Control?	4)
5) How many individuals does your TB control program cover?	5)
6) How many Tuberculin Skin Tests (TST) are performed each year in your program?	6)
7) Is the number of TSTs performed each year increasing, decreasing or staying the same?	7)
8) If the number of TSTs performed each year is changing, why?	8)
Part C: Your Opinions on the Tuberculin Skin Test:	
9) What are the main disadvantages with the TST?	9) List below: a) b) c) d)
10) Are there any advantages of the TST?	10) List below: a) b) c) d)
11) Would you like to see the TST replaced?	11)

Part D: Opinions on the QuantiFERON® TB Test	
12) Based on the assumptions given above, would you adopt the QuantiFERON® TB test to: a) Completely replace the Tuberculin Skin Test? b) Use in conjunction with the Tuberculin Skin Test?	12) a) b)
13) If you answered "yes" to either part of question 12, please estimate the numbers of QuantiFERON® TB tests that would be performed in your program in the years: a) 2000 (year of FDA approval)? b) 2001? c) 2002? d) 2003? e) Maximum number each year if not reached by 2003?	13) a) b) c) d) e)
14) What are the main advantages of the QuantiFERON® TB test?	14) List below: a) b) c) d)
15) Do you see any disadvantages in the QuantiFERON® TB test?	15) List Below: a) b) c) d)
Part E: Concluding Questions and Comments:	
16) Please use this box to insert any additional comments for our consideration or questions that you would like answered. We welcome suggestions on ways to promote adoption of this test.	
17) Can you suggest any other Military Personnel involved in TB control that should participate in this survey?	
18) At the suggestion of Colonel Patrick Kelley we intend to make presentations on the QuantiFERON® TB test results (performance and financial analysis) to the AFEB and JPMPG committees. In your opinion are there other bodies within the Military which should be made aware of this new TB test?	
19) Would you like a copy of the survey results?	
20) Would you like me to send a copy of the survey results to anybody else in the Military (insert name and address)?	
End of Survey: Thank you for your participation.	

Appendix D: Responses Received for the Survey Distributed During Stage 3

Question	MAJ. LISA KEEP	MAJ. ROHIT KATIAL	MAJ. WILLIAM CORR	LTC DAVID NIEBUHR
Your Name?	1) Lisa Keep	1) MAJ Rohit Katial, MD.	1) William P. Corr, MAJ, MC	1) LTC David Niebuhr
Your Title?	2) Deputy Director, Preventive Medicine Residency Program, WRAIR	2) Chief, Clinical and Laboratory Immunology Service	2) Chief, Preventive Medicine and Medical Training, Surgeon's Office, US Army Special Operations Command	2) Chief, Preventive Medicine Service, Ireland Army Community Hospital
Your Mailing Address?	3) WRAIR, Building 503 – Room 2A21, Division of Preventive Medicine, Robert Grant Road, Forest Glen Annex, Washington, DC 20307-5100	3) Rohit Katial, MD, Walter Reed Army Medical Center, Allergy/Immunology Clinic, Washington, DC. 20307	3) USASOC AOMD (Surgeon's Office, Prev Med), Ft. Bragg, NC 28314	3) USA MEDDAC, MCXM-PM, Fort Knox, KY 40121
What is your responsibility for TB control?	4) Currently none; formerly Chief of PM, Ft. Drum, NY (similar to Director of Public Health at a small PH Dept); will answer survey for my time at Ft. Drum.	4) We administer all PPD skin test in this area and deliver all immunizations	4) Oversight of prevention efforts in the United States Army Special Operations Command	4) Chair, Infection Control Committee overall responsibility for Knox TB control program
How many individuals does your TB control program cover?	5) Approx 10,000	5) Uncertain	5) 21000	5) 800+ MEDDAC, 15,000 basic trainees per yr

Question	MAJ. LISA KEEP	MAJ. ROHIT KATIAL	MAJ. WILLIAM CORR	LTC DAVID NIEBUHR
How many Tuberculin Skin Tests (TST) are performed each year in your program?	6) Difficult to estimate, annually on approx 200 health care workers, post-deployment tests done on about 8,000 soldiers after deployment to Haiti in 1995. In years when only small numbers deploy, probably about 1,000-2,000. If there were a requirement for every-2-year testing, about 5,000 should be done annually.	6) 7000/year	6) 13000	6) 20,000+
Is the number of TSTs performed each year increasing, decreasing, or staying the same?	7) Varies with deployment. Currently about 600-700 soldiers from Ft. Drum are deployed to Bosnia for 6-month tours. Smaller numbers, 10-100 at a time, deploy worldwide routinely. Pre- and post-deployment tests should be done for most if not all of these soldiers.	7) About the same	7) Slowly increasing	7) Increasing
If the number of TSTs performed each year is changing, why?	8) See above.		8) Increased command emphasis, especially in our reservists who go overseas	8) Increasing number of basic trainees

Question	MAJ. LISA KEEP	MAJ. ROHIT KATIAL	MAJ. WILLIAM CORR	LTC DAVID NIEBUHR
What are the main disadvantages with the TST?	9) List below: a) Difficult to place b) Difficult to read c) Difficult to document d) Difficult to interpret	9) List below: a) Return visit b) Variability in reading c) Non-specific reactivity d) Variability in technique	9) List below: a) Having to come back to have it read b) Subjective interpretation c) Boosting Effect d) Other false positive results	9) List below: a) Subjective results b) Low sensitivity c) Two patient visits d) Booster effect
Are there any advantages of the TST?	10) List below: a) Familiarity, for those who know enough to be familiar with it. b) It exists.	10) List below: a) Inexpensive b) Fairly easy to perform with correct training	10) List below: a) Known and accepted by soldiers	10) List below: a) Historical experience b) Good specificity
Would you like to see the TST replaced?	11) Yes!	11) I like the idea of an additional testing methodology.	11) Yes, I would like to see the TST replaced.	11) Yes
Based on the assumptions given above, would you adopt the QuantiFERON® TB test to:	12)	12)	12)	12)
Completely replace the Tuberculin Skin Test?	12a) Yes	12a)	12a) Completely replace (if it is as good as it seems to be)	12a) Yes, if FDA approved
Use in conjunction with the Tuberculin Skin Test?	12b) No	12b) yes	12b)	12b) Yes, as part of a clinical trial
If you answered "yes" to either part of question 12, please estimate the numbers of QuantiFERON® TB tests that would be performed in your program in the years:	13) See above for difficulties with estimating these numbers.	13) Not sure	13)	13)
2000 (year of FDA approval)?	13a) 1,500 (5,000 if every 2 yr testing)	13a)	13a)	13a) 800

Question	MAJ. LISA KEEP	MAJ. ROHIT KATIAL	MAJ. WILLIAM CORR	LTC DAVID NIEBUHR
2001?	13b) same	13b)	13b)	13b) 15,000
2002?	13c) same	13c)	13c)	13c) 15,000
2003?	13d) same	13d)	13d)	13d) 15,000
Maximum number each year if not reached by 2003?	13e) same	13e)	13e)	13e) 15,000
What are the main advantages of the QuantiFERON® TB test?	14) List below: a) Single contact with patient b) Done by trained lab personnel c) Documentation can be in lab database d) Consistent interpretation	14) List below: a) Different immunologic mechanism b) In-vitro assay c) Differentiates between MAC and tb d) Response does not modulate over time	14) List below: a) The patient doesn't have to come back to for the results to be evaluated b) Quantifiable results	14) List below: a) Quantifiable b) Increased sensitivity c) One patient visit
Do you see any disadvantages in the QuantiFERON® TB test?	15) List Below: a) Requires lab equipment and personnel, so may not be feasible for locations with small numbers of tests to run. b) Can't draw and hold/ship blood or use stored serum to run test.	15) List Below: a) Cost, technique, reproducibility	15) List Below: a) Unknown track record in US b) Cost	15) List Below: a) Cost reagents b) Lab workload
Please use this box to insert any additional comments for our consideration or questions that you would like answered. We welcome suggestions on ways to promote adoption of this test.	16)	16)	16)	16)

Question	MAJ. LISA KEEP	MAJ. ROHIT KATIAL	MAJ. WILLIAM CORR	LTC DAVID NIEBUHR
Can you suggest any other Military Personnel involved in TB control that should participate in this survey?	17) CAPT Liz Ledbetter, ekledbetter@nepmu5.med.navy.mil CDR Stephen Hooker, hookersg@iiimef.usmc.mil CAPT Dave Trump, david.trump@ha.osd.mil MAJ Eric Lund, eric.lund@amedd.army.mil	17)	17) Suggest that the personnel that actually place and the read the tests be consulted. For starters, the major training installations medical reception stations may provide good feedback (for the Army, that would be Ft. Benning, Ft. Jackson, Ft LeonardWood, Ft. Knox, Ft. Sill)	17)
At the suggestion of Colonel Patrick Kelley we intend to make presentations on the QuantIFERON® TB test results (performance and financial analysis) to the AFEB and JRMFG committees. In your opinion, are there other bodies within the Military which should be made aware of this new TB test?	18) None that I am aware of.	18)	18) Pathology/Laboratory Personnel. They need to be informed.	18) TRADOC surgeon, USAREC surgeon
Would you like a copy of the survey results?	19) Yes	19) Yes	19) Yes, please	19) No
Would you like me to send a copy of the survey results to anybody else in the Military (insert name and address)?	20)	20)	20)	20)

Question	LCDR MARGARET RYAN	LtCOL JAMES NEVILLE	COL. CRAIG URBAUER
Your Name?	1) Margaret Ryan, MD, MPH, LCDR, MC, USN	1) James Neville	1) Craig L. Urbauer, Colonel, MC
Your Title?	2) Medical Epidemiologist	2) Chief, Force Health Protection and Surveillance Branch	2) Command Surgeon, U.S. Army Reserve Command
Your Mailing Address?	3) Emerging Illness Division, Naval Health Research Center, PO Box 85122, San Diego, CA 92186	IERA/RSRH, 2513 Kennedy Circle, Brooks AFB, TX 78232	3) Headquarters, USARC, ATTN: AFRC-MD, 1401 Deshler St., SW, Fort McPherson, GA 30330-2000, (404) 464-8212 urbauerc@usarc-emh2.army.mil
What is your responsibility for TB Control?	4) Consultant to Navy Recruit Training Command, Great Lakes (as past Head of Preventive Medicine there)	4) Oversee central office where AF data is analyzed; currently studying AF TB control policies, especially screening. I don't currently have direct control over screening or treatment procedures.	4) N/A
How many individuals does your TB control program cover?	5) At Great Lakes, 50,000 new recruits each year (also training staff and health care workers on base)	5) 800,000+ for 1998 (including active duty and dependents)	5) N/A
How many Tuberculin Skin Tests (TST) are performed each year in your program?	6) Nearly 50,000 on new recruits	6) AF-wide estimate: 229,171 in 1997; 255,450 in 1998	6) N/A
Is the number of TSTs performed each year increasing, decreasing or staying the same?	7) Staying approximately the same	7) Roughly the same, but hard to predict, maybe a slight increase	7) N/A

Question	LCDR MARGARET RYAN	LtCOL JAMES NEVILLE	COL. CRAIG URBAUER
8) NA	8) NA	8) Increasing deployments may increase the number of tests done, however the services are still getting smaller, so maybe there will be fewer tests done; hard to predict.	8) N/A
9) List below: a) Need to return to read b) Subjective component to reading c) Difficulty with recording/tracking results d) Difficulty with creating an automated database of results	9) List below: a) Need to return to read b) Subjective component to reading c) Difficulty with recording/tracking results d) Difficulty with creating an automated database of results	9) List below: a) Patient must return b) "can't" be done on Thursday (or Friday if Monday is a holiday) c) variable interpretation skills d) needle in arm e) Likelihood of developing active TB is relatively low if + TST f) Different cut-offs for different risk categories g) Imprecise detection of true TB vs non-human pathogen H) h) Screening low risk population, decreases predictive value of a positive test	9) N/A
10) List below: a) Accepted standard; described well in CDC recommendations b) Very sensitive for TB infection if 10mm criteria used c) Long, well-described hx of use	10) List below: a) Accepted standard; described well in CDC recommendations b) Very sensitive for TB infection if 10mm criteria used c) Long, well-described hx of use	10) List below: a) Long history, well imbedded in practice b) Well studied c) Relatively easy in deployed or austere setting	10) N/A
11) Only if replaced by a test with at least equal sensitivity and specificity	11) Only if replaced by a test with at least equal sensitivity and specificity	11) Yes	11) N/A

Question	LCDR MARGARET RYAN	LtCOL JAMES NEVILLE	COL. CRAIG URBAUER
Based on the assumptions given above, would you adopt the Quantiferon® TB test to:	12) I would adopt test only IF assumptions were true. I do not believe the critical assumption on performance is true; i.e., I do not believe the test has been demonstrated to have equal or better sensitivity and specificity to the PPD standard.	12)	12) CA
Completely replace the Tuberculin Skin Test?	12a)	12a) as a screening tool, yes	12a) CA
Use in conjunction with the Tuberculin Skin Test?	12b)	12b) no, except some special cases, maybe, depending on further studies	12b)CA
If you answered yes to either part of question 12, please estimate the numbers of Quantiferon® TB tests that would be performed in your program in the years:	13) [Approx 50,000 per year at Great Lakes, as previously stated]	13) Total guess, but assuming 240,000 tests done overall per year . . .	13) CA
2006 (year of FDA approval)?	13a)	13a) 30%	13a) CA
2007?	13b)	13b) 60%	13b) CA
2008?	13c)	13c) 95%	13c) CA
2009?	13d)	13d) 100%	13d) CA
Maximum number each year if not reached by 2009?	13e)	13e)	13e) CA
What are the main advantages of the Quantiferon® TB test?	14) List below: a) As a more "classic" lab test, results could be attained without repeat patient contact. Results could be	14) List below: a) No return required b) No judgement of reaction size c) Potential for combining with other blood tests	14) CA

Question-	LCDR MARGARET RYAN	LtCOL JAMES NEVILLE	COL. CRAIG URBAUER
	automatically entered in a database which could be accessed for patient follow-up and critical epidemiologic analyses.		
Do you see any disadvantages in the Quantiferon® TB test?	15) List Below: a) As lab tests go, rather complicated, involving testing of both blood and sera; lots of lab hands-on time. b) Requires overnight incubation; not "fast". c) Fails to reveal remote infections found with two-step (boosting) PPD tests. This should be considered a DISADVANTAGE, contrary to your info sheet. d) Cost? (I have not yet seen evidence that the test will be just as cost-effective as PPD testing)	15) List Below: a) New test requires knowledgeable application, training for docs, techs (sens/spec, PPV, NPV, etc) b) Patient has to go to lab c) Some patients hate blood draws d) What's the long-term likelihood of disease with a positive test? e) May be logistically more difficult in austere settings	15) CA
Please use this box to insert any additional comments for our consideration or questions that you would like answered. We welcome suggestions on ways to promote adoption of this test.	16) I am very interested in seeing all the data – published and unpublished – on sensitivity and specificity of the test. Anything that could be done to increase sensitivity, in particular, would make the test potentially very useful in a high risk population.	16) My main concern is the level of understanding of sensitivity and specificity. This would be used as a screening test, and there are many examples of inappropriate screening tests. Will there be different cutoff levels for different risk categories? Are all costs	16) . I am the Surgeon for the US Army Reserve Command (USARC). The USARC is subordinate to the US Army Forces Command (FORSCOM), and for many issues follows FORSCOM guidance. The US Army Reserve (USAR) does not provide any health care. The vast majority of its soldiers are traditional reservists who take personal responsibility for their own health, given that they are soldiers for only 39 days annually. Full time USAR Soldiers (AGR soldiers) obtain their health care from the USA MEDCOM

Questions	LCDR MARGARET RYAN	LtCOL JAMES NEVILLE	COL. CRAIG URBAUER
		considered in the analysis?	(TRICARE). USAR soldiers who are on Annual Training for 15 days, or mobilized for 30 days or longer are Active Duty soldiers, and the US Army provides all health care during this time, and is responsible for follow up care of any medical condition which might occur while upon Active Duty. Specifically regarding tuberculosis screening and follow up, if a USAR soldier returns from an area identified by FORSCOM as being a tuberculosis endemic area, that soldier receives a PPD at the demobilization site at Fort Benning, GA
Can you suggest any other Military Personnel involved in TB control that should participate in this survey?	17) Although Navy is well-represented already, perhaps CDR Brian Murphy from NEHC would also like to respond.	17) Infectious Disease consultant to the AF SG: LtCol Greg Melcher, gregory.melcher@60mdg.travis.af.mil , Maybe a lab consultant, although I'm not sure who that would be	17) None
At the suggestion of Colonel Patrick Kelley we intend to make presentations on the QuantiFERON® TB test results (performance and financial analysis) to the AFEB and JPMPG committees. In your opinion are there other bodies within the Military which should be made aware of this new TB test?	18) When CDR Murphy is aware, you will have also made the Navy Epidemiology Board (an advisory panel to CO, NEHC) aware.	18) Depending on the results. Assuming the results are favorable and the test will be recommended as a replacement for IPPD, then the entire medical community will need education. For the AF, the public health, aerospace medicine and flight medicine communities will need particular attention. Military Medicine? Newsletters, training courses, etc.	18)
Would you like a copy of the survey results?	19) Yes	19)Yes	19)
Would you like me to send a copy of the survey results to anybody else in the Military?	20)	20)	20)

Question	CAPT DAVID TRUMP	COL. DANA BRADSHAW	CAPT KEVIN HANSON	CDR. STEPHEN G. HOOKER
Your Name?	1) David Trump, MD, MPH, CAPT, MC, USN	1) Col Dana Bradshaw	1) Kevin Hanson, CAPT MC USN (FS)	1) Stephen G. Hooker
Your Title?	2) Program Director, Preventive Medicine and Surveillance	2) Chief, Preventive Medicine	2) Director, GPM Residency, USUHS	2) Preventive Medicine Officer III Marine Expeditionary Force
Your Mailing Address?	3) OASD (Health Affairs), 5111 Leesburg Pike, Suite 810, Falls Church, VA 22041-3206	3) AFMOA/SGOP, 110 Luke Avenue, Room 405, Bolling AFB, DC 20332-7050	3) USUHS, Rm A1040A, 4301 Jones Bridge Rd, Bethesda, MD 20814-4799	3) PSC 559 Box 5515, FPO AP 96377
What is your responsibility for TB Control?	4) DoD policy development and oversight for military preventive medicine and public health	4) Direct USAF TB program policy	4) None currently. Residency training	4) Primarily in overseeing implementation, consultation, and compliance
How many individuals does your TB control program cover?	5) 1.4 million active duty plus Reserve component personnel, civilian workers, family members, and other beneficiaries (total beneficiary population is in excess of 5 million).	5) Approximately 600,000	5) N/A	5) 21,000
How many Tuberculin Skin Tests (TSTs) are performed each year in your program?	6) CA	6) 250,000 (based on 1998 figures)	6) N/A	6) 21,000
Is the number of TSTs performed each year increasing, decreasing or staying the same?	7) CA	7) decreasing	7) N/A	7) Same
If the number of TSTs performed each year is changing, why?	8) NA	8) Due to decreasing number of personnel	8) N/A	8) N/A

Question	CAPT DAVID TRUMP	COL. DANA BRADSHAW	CAPT KEVIN HANSON	CDR. STEPHEN G. HOOKER
What are the main disadvantages with the TST?	<p>9) List below: a) Requires two visits 48-72 hours apart b) Interpretation of reactions produces a semi-subjective measurement c) Administration of ID injection subject can be flawed by training and technical challenges. d) Observed reaction subject to cross-reaction with nontuberculous mycobacteria. E) Good serial screening program requires two-step initial TST f) Unwarranted concern over booster response</p>	<p>9) List below: a) False positives b) Reader variability c) Loss to F/U (placed/not read) d) Time</p>	<p>9) List below: a) QA on technique b) QA on reading it c) Losses to follow up d) Time consuming (2 visits)</p>	<p>9) List below (a) Low Specificity (b) Low Sensitivity (c) Followup visit required (d) Not useful in previously infected</p>
Are there any advantages of the TST?	<p>10) List below: a) Established policy b) Existing database of published literature and recommendations on interpretation of reaction and appropriate management. c) Cheap d) Administration and interpretation if done by informed, skilled practitioner is relatively cheap.</p>	<p>10) List below: a) Inexpensive b) Easy to place c) No blood draw d) Familiar, well-researched test</p>	<p>10) List below: a) Best available, no particular advantage</p>	<p>10) List below: (a) Simple (b) Low invasiveness (c) Inexpensive (d) Well tolerated</p>
Would you like to see the TST replaced?	<p>11) Yes</p>	<p>11) Depends on what the alternative is.</p>	<p>11) Yes, we need a simpler, less technique-dependent test with good sensitivity and specificity.</p>	<p>11) If there is a better test that is cost effective.</p>

Question	CAPT DAVID TRUMP	COL. DANA BRADSHAW	CAPT KEVIN HANSON	CDR. STEPHEN G. HOOKER
Based on the assumptions given above, would you adopt the Quantiferon® TB test to:	12)	12)	12)	12)
Completely replace the Tuberculin Skin Test?	12a) Yes	12a) Depends on the test specificity and sensitivity.	12a) If and only if sens and spec are at least equal	12a) No
Use in conjunction with the Tuberculin Skin Test?	12b) No	12b) If it helped reduce false-positives	12b) Do not see an advantage to this	12b) Yes
If you answered "yes" to either part of question 12, please estimate the numbers of Quantiferon® TB tests that would be performed in your program in the years:	13)	13) Difficult to assess, as we are reviewing our actual risk-based conversion rates. This will drive whom we test, and test frequency. If we kept current screening frequency and used as replacement test, would use up to 250,000 annually. If used only as confirmatory test to reduce false-positives, might be only 6,500 annually.	13) N/A, but we have an annual testing requirement throughout much of Navy and Marine Corps	13)
2000 (year of FDA approval)?	13a) CA	13a)	13a)	13a) 630
2001?	13b) CA	13b)	13b)	13b) 630
2002?	13c) CA	13c)	13c)	13c) 630
2003?	13d) CA	13d)	13d)	13d) 630
Maximum number each year if not reached by 2003?	13e) CA	13e)	13e)	13e) 630

Question	CAPT DAVID TRUMP	COL. DANA BRADSHAW	CAPT KEVIN HANSON	CDR. STEPHEN G. HOOKER
What are the main advantages of the QuantiFERON® TB test?	14) List below: a) Objective test result (I assume) b) Single visit c) For the patient, a new lab test will have more credibility as a marker of infection than the “good old” skin test reaction (can’t figure out if that is fortunate or unfortunate) d) Potential for providing a Method to track response to chemopreventive therapy	14) List below: a) No loss to F/U b) No reader variability c) Standardized, lab-based test d) Less cross-reaction with other mycobacterial species	14) List below: a) Minimal training requirement b) No follow up required after 48 hrs	14) List below: (a) Greater Sens & Spec (b) Can use in previously infected (c) Can be used on immuno-compromised
Do you see any disadvantages in the QuantiFERON® TB test?	15) List Below: a) Cost of test b) Added burden on laboratory services including additional personnel c) Educating physicians, nurses, and large technician force on new procedure, documentation requirements, and interpretation d) Uncertainty of how QuantiFERON TB results need to be interpreted with respect to diagnosis of clinical disease, diagnosis and management of infection, evaluation of effectiveness of response to treatment/chemoprevention, re-infection, serial screening, etc.	15) List Below: a) Requires blood draw b) What are the specificity & sensitivity? c) Cost?	15) List Below: a) Issues are cost, sens/spec	15) List Below: (a) Invasive – less tolerated (b) Handling blood (c) Less versatile –e.g. use in field conditions (d) Dependent on more lab materials

Question	CAPT DAVID TRUMP	COL. DANA BRADSHAW	CAPT KEVIN HANSON	CDR. STEPHEN G. HOOKER
<p>Please use this box to insert any additional comments for our consideration or questions that you would like answered. We welcome suggestions on ways to promote adoption of this test.</p>	<p>16) Military public health practice has worked best when it is compatible with national standards of public health practice (e.g., following CDC recommendations). If we deviate from national standards of practice, we have a tough time getting buy-in from providers and specialists (ID and pulmonary medicine). Large scale adoption of a new screening technology for tuberculosis in the military has to be built on recommendations for screening and management from CDC/ACET, pulmonary medicine/infectious disease specialty organizations and others. It would help to have a US Preventive Services Task Force review and evidence-based recommendation on the utility of screening.</p>	<p>16) a) What is meant by a test 'equivalent in efficacy' to the TBST? b) Am concerned about the cost relative to current methods.</p>	<p>16)</p>	<p>16) Thank you for your work and efforts, and allowing me to participate in this survey.</p>

Question	CAPT DAVID TRUMP	COL. DANA BRADSHAW	CAPT KEVIN HANSON	CDR. STEPHEN G. HOOKER
Can you suggest any other Military Personnel involved in TB control that should participate in this survey?	17) Yes, a) CAPT Thad Zadajowicz, MC, USN, Navy Environmental Health Center, Norfolk, VA, b) CAPT J.D. Malone, MC, USN, Naval Medical Center, San Diego, CA c) CAPT Joe Malone, MC, USN, Naval Medical Center, Portsmouth, VA d) Surgeons General Specialty Leaders in Pulmonary Medicine and Infectious Diseases, and e) Surgeons General Specialty Leaders in Laboratory Sciences, especially clinical laboratories	17)	17) No	17) No
At the suggestion of Colonel Patrick Kelley we intend to make presentations on the QuantiFERON® TB test results (performance and financial analysis) to the AFEB and JPMPG committees. In your opinion are there other bodies within the Military which should be made aware of this new TB test?	18) Military/uniformed services chapters of national pulmonary medicine and infectious disease specialty organizations	18)	18) Good start. Further military contact should be contingent on recommendations from these organizations.	18) Navy Epidemiology Board
Would you like a copy of the survey results?	19) Yes	19) Yes	19) No	19) Yes
Would you like me to send a copy of the survey results to anybody else in the Military (insert name and address)?	20) No	20)	20) No	20) No